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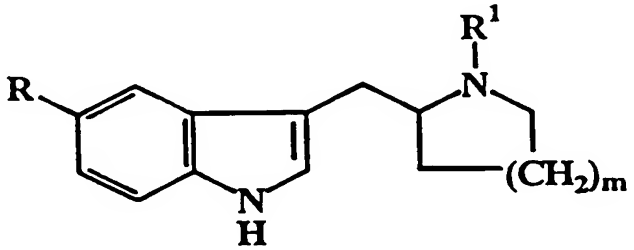
(54) Title: INDOLE DERIVATIVES AS 5-HT1-LIKE AGONISTS



(I)

(57) Abstract

A compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R is phenyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, furyl or thienyl, all of which may be optionally substitued by halo, C_1-C_4 alkyl, C_1-C_4 alkoxy or a group of the formula: -X-R^2; R^1 is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, C_3-C_6 alkenyl or C_3-C_6 alkynyl, said alkyl group being optionally substituted by C_3-C_7 cycloalkyl, C_3-C_7 cycloalkyloxy, OH, C_1-C_6 alkoxy, $CONR^3R^4$, $SO_2NR^3R^4$, COR^5, SOR^5, SO_2R^5, CO_2R^6, aryl, aryloxy, aryl(C_1-C_6)alkoxy or heteroaryl, said alkenyl group being optionally substituted by aryl and said cycloalkyl group being optionally substituted by OH; the cycloalkyl and cycloalkenyl groups of the foregoing groups being optionally linked to the N-atom by a C_1-C_2 alkylene moiety; R^2 is COR^7, CO_2R^7, SOR^7, SO_2R^7, $CONR^3R^4$, $SO_2NR^3R^4$, $NHCOR^7$, $NHCONR^3R^4$, $NHSO_2R^7$, $NHSO_2NR^3R^4$, OH or CN; R^3 and R^4 are either each independently selected from H, C_3-C_7 cycloalkyl and C_1-C_6 alkyl, said alkyl group being optionally substituted by C_3-C_7 cycloalkyl or aryl, or R^3 and R^4 taken together represent C_3-C_6 alkylene optionally interrupted by O, $S(O)_n$, NH or $N(C_1$-C_6 alkyl); R^5 is C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkyl(C_1-C_6)alkylene, aryl(C_1-C_6)alkylene or aryl; R^6 is C_1-C_6 alkyl, C_3-C_7 cycloalkyl or aryl(C_1-C_6)alkylene; R^7 is C_1-C_6 alkyl; X is a direct link or C_1-C_7 alkylene; m is 1 or 2; and n is 0, 1 or 2; are selective 5-HT_1-like receptor agonists useful in the treatment of migraine, cluster headache, chronic paroxysmal hemicrania and headache associated with vascular disorders.

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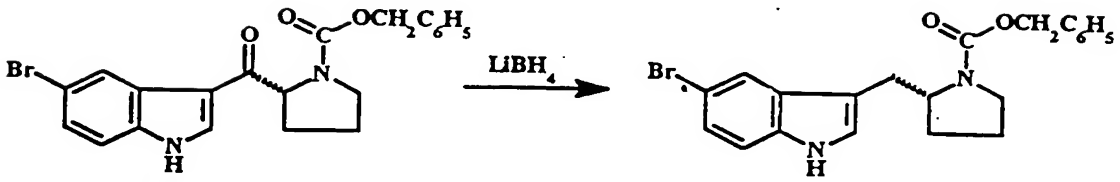
PREPARATION 35B

3-(1-Benzyloxycarbonylpyrrolidin-2(R)-ylmethyl)-5-bromo-1H-indole



(see Preparation 27A)

3-(1-Benzyloxycarbonylpyrrolidin-2(R)-ylcarbonyl)-5-bromo-1H-indole (0.67g, 1.57mmol) (see Preparation 35) was dissolved in dry tetrahydrofuran (20ml) and, at room temperature, under nitrogen, lithium borohydride (2M solution in tetrahydrofuran; 1.2ml, 2.4mmol) was added. The reaction mixture was stirred at room temperature for 3 hours, heated under reflux for 16 hours, then allowed to cool to room temperature. 2N Hydrochloric acid (10ml) was added dropwise and the reaction mixture then partitioned between ethyl acetate and water. The separated organic phase was washed with saturated aqueous sodium bicarbonate solution (twice) and brine (once), dried (Na_2SO_4), and evaporated under reduced pressure to give a colourless oil. Purification by column chromatography on silica gel, eluting with dichloromethane, gave the title compound as an oil (0.32g). Found: C,59.94; H,5.07; N,6.58. $C_{21}H_{21}BrN_2O_2.1/10CH_2Cl_2$ requires: C,60.08; H,5.07; N,6.64%.

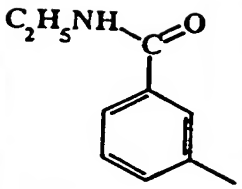
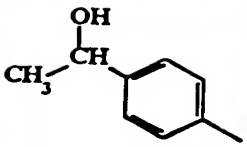
PREPARATION 35

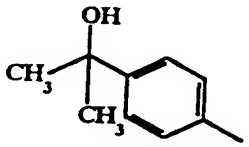
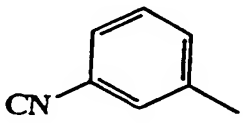
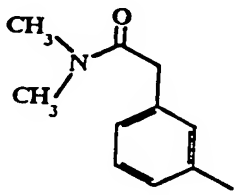
3-(1-Benzyloxycarbonylpyrrolidin-2(R)-ylcarbonyl)-5-bromo-1H-indole

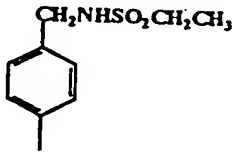
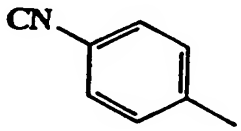
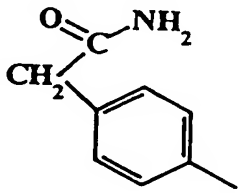
To a stirred solution of N-benzyloxycarbonyl-D-proline (1.0 g) in anhydrous dichloromethane (2 ml) and N,N-dimethylformamide (1 drop) was added oxalyl chloride (0.5 ml) and the resulting solution was stirred at room temperature for 1.5 hours. The solution was evaporated under reduced pressure and remaining solvent was removed under high vacuum to give the acid chloride of N-benzyloxycarbonyl-D-proline.

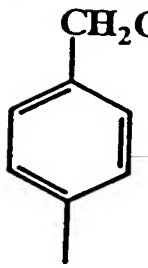
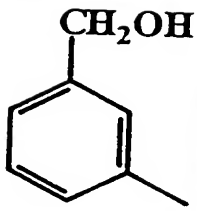
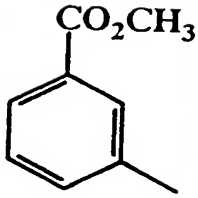
In a separate flask a solution of ethylmagnesium bromide (1.4 ml of a 3M solution in diethyl ether) was added dropwise over 5 minutes to a stirred solution of 5-bromoindole (0.75 g) in dry diethyl ether (18 ml). The mixture was stirred at room temperature for 10 minutes, heated under reflux for 2 hours, then cooled to -30°C. A solution of the above acid chloride of N-benzyloxycarbonyl-D-proline in dry diethyl ether (4 ml) was then added dropwise with stirring and stirring was continued for a further 1 hour. Diethyl ether (12.5 ml) and saturated aqueous sodium bicarbonate (6.5 ml) were added and the reaction was allowed to warm to room temperature. Stirring was continued for a further 10 minutes and the mixture was filtered. The solid was washed with ethyl acetate and the combined filtrate and washings were washed with water then brine and dried ($MgSO_4$). Evaporation of the solvent gave an oil which was chromatographed on silica gel. Elution with ethyl acetate gave, after combination and evaporation of the appropriate fractions, the title compound as a foam, (0.82 g). Found: C,58.85; H,4.51; N,6.38; $C_{21}H_{19}BrN_2O_3$ requires: C,59.02; H,4.48; N,6.56%.

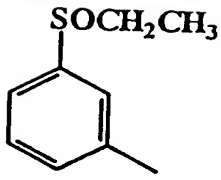
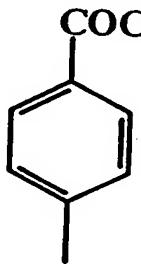
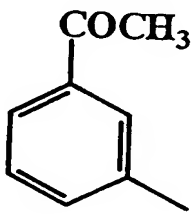
LRMS, m/z (relative intensity) = 428 [M+ with ^{81}Br] (5), 426 [M+ with ^{79}Br] (5), 224 (19), 222 (21), 204 (62), 160 (68), 91 (100).

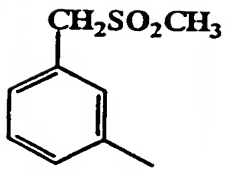
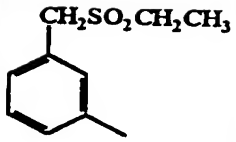
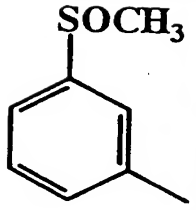
Prep No	R	Starting material (corresponding bromo- or iodo-benzene)	Analysis (%)	^{1}H-NMR ($CDCl_3$)
33		bromo-		δ = 0.85(t,9H), 1.10(t,6H), 1.20-1.45(m,9H), 1.50 (m,6H), 3.50(q,2H), 6.00(s,1H), 7.35 (dd,1H), 7.58 (d,1H), 7.60(d,1H), 7.85(s,1H).
34		bromo-		δ = 0.90(t,9H), 1.10(t,6H), 1.30 (m,6H), 1.40-1.55 (m,9H), 1.80(d,1H), 7.35(d,2H), 7.45 (d,2H).

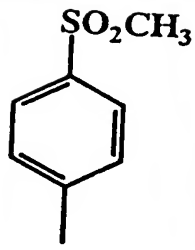
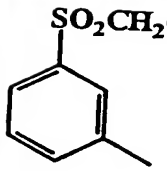
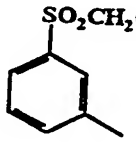
ep lo	R	Starting material (corresponding bromo- or iodo-benzene)	Analysis (%)	^{1}H-NMR ($CDCl_3$)
O		iodo-	-	δ = 0.90(t,9H), 1.10(t,6H), 1.30(m,6H), 1.40-1.60 (m,6H), 1.55 (s,6H), 7.35-7.45 (m,4H).
		bromo-	-	δ = 0.90(t,9H), 1.10(t,6H), 1.35 (m,6H), 1.50(m,6H), 7.40(dd,1H) 7.55 (d,1H), 7.70(d,1H), 7.75(s,1H).
		iodo-	Found: C,56.30; H,8.45; N,2.90; $C_{22}H_{39}NOSn.H_2O$ requires C,56.19; H,8.78; N,2.97.	δ = 0.90(t,9H), 1.10(t,6H), 1.35 (m,6H), 1.55(m,6H), 2.98(s,3H), 3.00 (s,3H), 3.75(s,2H), 7.15-7.45(m,4H).

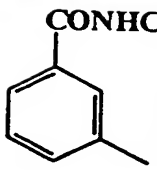
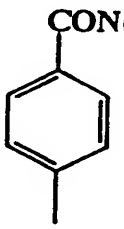
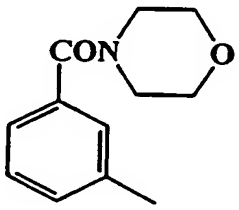
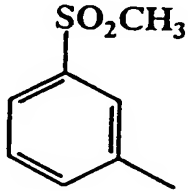
Prep No	R	Starting material (corresponding bromo- or iodo-benzene)	Analysis (%)	^{1}H-NMR ($CDCl_3$)
27		bromo-	Found: C,51.78; H,8.00; N,2.64; $C_{21}H_{39}NO_2SSn$ requires C,51.66; H,8.05; N,2.87.	δ = 0.88(t,9H), 1.05(t,6H), 1.20-1.40(m,9H), 1.50 (m,6H), 2.95 (q,2H), 4.30 (d,2H), 4.45 (m,1H), 7.28 (d,2H), 7.48(d,2H) ppm.
28		iodo-	-	δ = 0.90(t,9H), 1.10(t,6H), 1.30 (m,6H), 1.50 (m,6H), 7.55-7.65 (m,4H).
29		bromo-	-	δ = 0.90(t,9H), 1.10(t,6H), 1.30 (m,6H), 1.50 (m,6H), 3.60 (s,2H), 5.40 (s,1H), 5.65 (s,1H), 7.20 (d,2H), 7.45 (d,2H).

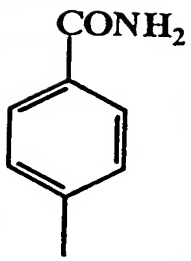
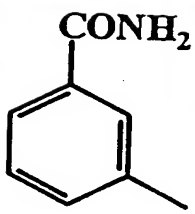
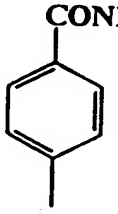
Prep No	R	Starting material (corresponding bromo or iodo-benzene)	Analysis (%)	^{1}H-NMR ($CDCl_3$)
24		bromo-	Found: C,55.74; H,8.24; N,NIL; $C_{19}H_{34}SnO.1/5CH_2Cl_2$ requires: C,55.68; H,8.37; N,NIL.	δ = 0.90(t,9H), 1.10(t,6H), 1.40(m,6H), 1.60(m,7H), 4.65(d,2H), 5.30(s,2/5H), 7.45(d,2H), 7.50(d,2H) ppm.
25		iodo-	Found: C,56.82; H,8.45; N,NIL; $C_{19}H_{34}SnO$ requires: C,57.00; H,8.56; N,NIL.	δ = 0.88(t,9H), 1.05(t,6H), 1.35(m,6H), 1.55(m,6H), 4.68(d,2H), 7.08-7.50(m,4H) ppm.
26		bromo-	-	δ = 0.90(t,9H), 1.10(t,6H), 1.35(m,6H), 1.55(m,6H), 3.92(s,3H), 7.19(dd,1H), 7.65(d,1H), 7.95(d,1H), 8.13(s,1H) ppm.

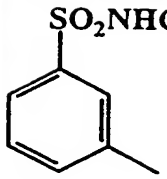
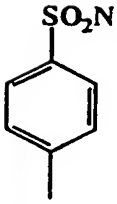
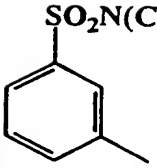
Prep No	R	Starting material (corresponding bromo- or iodo- benzene)	Analysis (%)	^{1}H-NMR ($CDCl_3$)
21		bromo-	-	δ = 0.90(t,9H), 1.10(t,6H), 1.20(t,3H), 1.35(m,6H), 1.55(m,6H), 2.78(m,1H), 2.84(m,1H), 7.40-7.65 (m,4H) ppm.
22		iodo-	-	δ = 0.90(t,9H), 1.10(t,6H), 1.35(m,6H), 1.52(m,6H), 2.60(s,3H), 7.58(d,2H), 7.88(d,2H) ppm.
23		bromo-	Found: C,58.61; H,8.24; N,NIL; $C_{20}H_{34}OSn$ requires: C,58.71; H,8.37; N,NIL.	δ = 0.87(t,9H), 1.10(t,6H), 1.35(m,6H), 1.55(m,6H), 2.60(s,3H), 7.40(dd,1H), 7.65(d,1H), 7.88(d,1H), 8.07(s,1H) ppm.

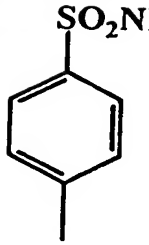
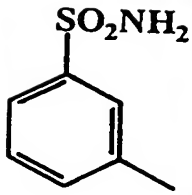
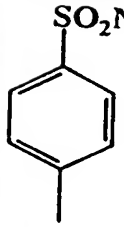
Prep No	R	Starting material (corresponding bromo- or iodo-benzene)	Analysis (%)	^{1}H-NMR ($CDCl_3$)
18		bromo-	-	δ = 0.90(t,9H), 1.05(t,6H), 1.35(m,6H), 1.55(m,6H), 2.75(s,3H), 4.12(s,2H), 7.35-7.50 (m,4H) ppm.
19		bromo-	-	δ = 0.88(t,9H), 1.08(t,6H), 1.20-1.40 (m,9H), 1.55(m,6H), 2.82(q,2H), 4.20(s,2H), 2.30-2.55 (m,4H) ppm.
20		bromo-	-	δ = 0.90 (t,9H), 1.10(t,6H), 1.35(m,6H), 1.55(m,6H), 2.75(s,3H), 7.40-7.60 (m,3H), 7.70 (s,1H) ppm.

Prep No	R	Starting material (corresponding bromo- or iodo-benzene)	Analysis (%)	^{1}H-NMR ($CDCl_3$)
15		bromo-	Found: C,51.37; H,7.62; N,NIL; $C_{19}H_{34}O_2SSn$ requires: C,51.26; H,7.70; N,NIL.	δ = 0.90(t,9H), 1.10(m,6H), 1.35(m,6H), 1.55(m,6H), 3.10(s,3H), 7.70(d,2H), 7.90(d,2H) ppm.
16		bromo-	-	δ = 0.90(t,9H), 1.10(m,9H), 1.35(m,6H), 1.55(m,6H), 3.10(q,2H), 7.50(dd,1H), 7.75(d,1H), 7.80(d,1H), 7.95(s,1H) ppm.
17		bromo-	-	δ = 0.90(t,9H), 1.00(t,3H), 1.15(t,6H), 1.35(m,6H), 1.55(m,6H), 1.75(m,2H), 3.10(t,2H), 7.52(dd,1H), 7.75(d,1H), 7.85(d,1H), 8.00(s,1H) ppm.

Prep No	R	Starting material (corresponding bromo- or iodo-benzene)	Analysis (%)	^{1}H-NMR ($CDCl_3$)
11		bromo-	-	δ = 0.90(t,9H), 1.05(t,6H), 1.30(m,6H), 1.55(m,6H), 3.00(s,3H), 6.05(s,1H), 7.35(dd,1H), 7.55(d,1H), 7.65(d,1H), 7.85(s,1H) ppm.
12		bromo-	Found: C,57.23; H,8.45; N,3.05; $C_{21}H_{37}NOSn$ requires: C,57.56; H,8.51; N,3.20.	δ = 0.85(t,9H), 1.05(t,6H), 1.32(m,6H), 1.52(m,6H), 3.00(s,3H), 3.10(s,3H), 7.35(d,2H), 7.47(d,2H) ppm.
13		bromo-	Found: C,57.73; H,8.52; N,2.65; $C_{23}H_{39}NO_2Sn$ requires: C,57.52; H,8.18; N,2.92.	δ = 0.85(t,9H), 1.05(t,6H), 1.30(m,6H), 1.50(m,6H), 3.25-3.95 (m,8H), 7.25-7.40(m,2H), 7.45(s,1H), 7.50(d,1H) ppm.
14		bromo-	Found: C,51.09; H,7.50; N,NIL; $C_{19}H_{34}O_2SSn$ requires: C,51.26; H,7.70; N,NIL.	δ = 0.90(t,9H), 1.10(t,6H), 1.30(m,6H), 1.55(m,6H), 3.05(s,3H), 7.50(dd,1H), 7.72(d,1H), 7.85(d,1H), 8.00(s,1H) ppm.

Prep No	R	Starting material (corresponding bromo- or iodo-benzene)	Analysis (%)	^{1}H-NMR ($CDCl_3$)
8		bromo-	-	δ = 0.90(t,9H), 1.05(t,6H), 1.35(m,6H), 1.55(m,6H), 6.25(s,2H), 7.55(d,2H), 7.75(d,2H) ppm.
9		bromo-	-	δ = 0.90(t,9H), 1.05(t,6H), 1.35(m,6H), 1.55(m,6H), 5.90(s,1H), 6.05(s,1H), 7.40(dd,1H), 7.60(d,1H), 7.70(d,1H), 7.90(s,1H) ppm.
10		bromo-	-	δ = 0.88(t,9H), 1.05(t,6H), 1.30(m,6H), 1.50(m,6H), 3.00(m,3H), 6.15(s,1H), 7.50(d,2H), 7.67(d,2H) ppm.

Prep No	R	Starting material (corresponding bromo- or iodo-benzene)	Analysis (%)	^{1}H-NMR ($CDCl_3$)
5		bromo-	-	δ = 0.90(t,9H), 1.10(t,6H), 1.35(m,6H), 1.55(m,6H), 2.65(d,3H), 4.28(q,1H), 7.23(dd,1H), 7.68(d,1H), 7.75(d,1H), 7.95(s,1H) ppm.
6		bromo-	-	δ = 0.90(t,9H), 1.10(t,6H), 1.35(m,6H), 1.55(m,6H), 2.70(s,6H), 7.55-7.70 (m,4H) ppm.
7		bromo-	-	δ = 0.90(t,9H), 1.10(t,6H), 1.35(m,6H), 1.55(m,6H), 2.70(s,6H), 7.50(dd,1H), 7.65-7.75 (m,2H), 7.90(s,1H) ppm.

Prep No	R	Starting material (corresponding bromo- or iodo-benzene)	Analysis (%)	^{1}H-NMR ($CDCl_3$)
2		bromo-	-	δ = 0.90(t,9H), 1.10(t,6H), 1.55(m,6H), 4.82(s,2H), 7.62(d,2H), 7.84(d,2H) ppm.
3		bromo-	-	δ = 0.90(t,9H), 1.10(t,6H),1.35 (m,6H), 1.55(m,6H), 4.82(s,2H), 7.46(dd,1H), 7.68(d,1H), 7.85(d,1H), 8.00(s,1H) ppm.
4		bromo-	-	δ = 0.90(t,9H), 1.10(t,6H), 1.35(m,6H), 1.55(m,6H), 2.68(d,3H), 4.38(q,1H), 7.65(d,2H), 7.80(d,2H) ppm.

A mixture of 3-bromo-N,N-dimethylbenzamide (2.74 g, 12.01 mmol), tri-o-tolylphosphine (960 mg, 3.15 mmol), palladium (II) acetate (120 mg, 0.54 mmol), triethylamine (3.20 ml, 22.96 mmol) and hexa-n-butyldistannane (6.96 g, 4.6 ml, 12.00 mmol) in anhydrous acetonitrile (40 ml) was heated under reflux, under nitrogen, for 18 hours. The reaction mixture was then evaporated under reduced pressure and dichloromethane (25 ml) was added. The resultant solution was washed with aqueous sodium carbonate, dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography on silica gel eluting initially with hexane until the tri-o-tolylphosphine and unreacted hexabutyldistannane had been eluted and then with hexane/ethyl acetate (1:1) to afford, after combination and evaporation of the appropriate fractions, the title compound as a light brown oil, (1.90 g).
Found: C, 57.39; H, 8.41; N, 3.04; $C_{21}H_{37}NOSn$ requires:
C, 57.56; H, 8.51; N, 3.20%.
^{1}H-NMR ($CDCl_3$): δ = 0.90 (t,9H), 1.05 (t,6H), 1.30 (m,6H), 1.52 (m,6H), 2.95 (s,3H), 3.12 (s,3H), 7.30-7.38 (m,2H), 7.40-7.55 (m,2H) ppm.

PREPARATIONS 2 TO 34

The stannane derivatives of the following tabulated Preparations were prepared by similar methods to that of Preparation 1 using the appropriate substituted bromo- or iodobenzenes as the starting materials.

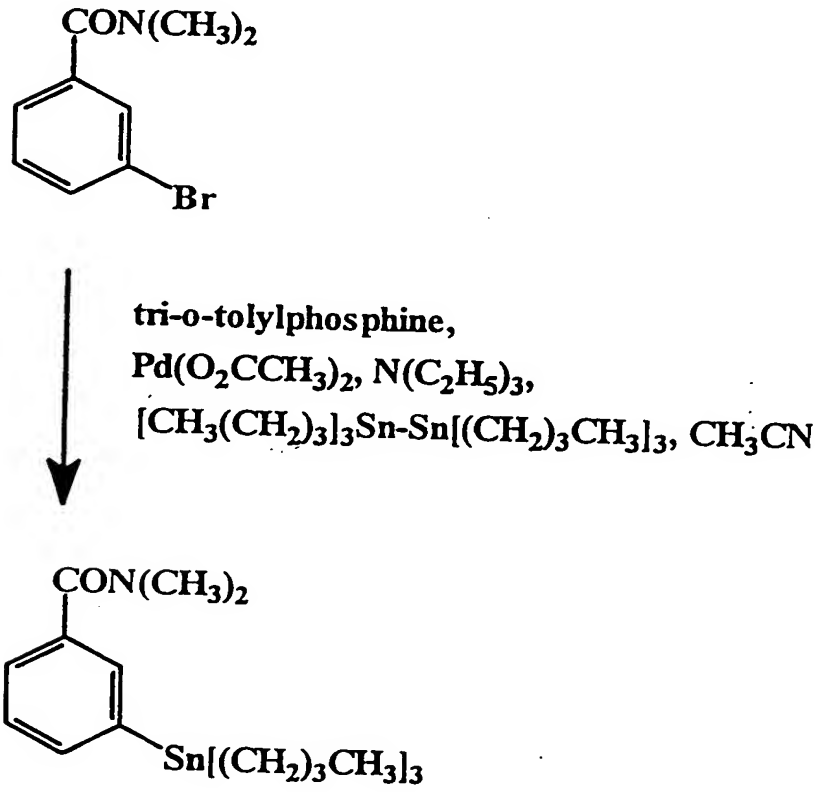
The derivatives have the general formula:-

$$RSn[(CH_2)_3CH_3]_3$$

The following Preparations illustrate the preparation of starting materials used in the preceding Examples:-

PREPARATION 1

3-N,N-Dimethylcarbamoylphenyltri-n-butylstannane



EXAMPLE 67

The in vitro evaluation of the "5-HT_1-like" receptor agonist activity of the compounds of the invention is carried out by testing the extent to which they mimic sumatriptan in contracting the isolated dog saphenous vein strip (P.P.A. Humphrey et al., Brit. J. Pharmacol., 1988, 94, 1123). This effect can be blocked by methiothepin, a known 5-HT antagonist. Sumatriptan is known to be useful in the treatment of migraine and produces a selective increase in carotid vascular resistance in the anaesthetized dog and a consequent decrease in carotid arterial blood flow. It has been suggested (W. Feniuk et al., Brit. J. Pharmacol., 1989, 96, 83) that this is the basis of its efficacy.

Biological activity

The following Table illustrates the in vitro activities for a range of the compounds of the invention on dog isolated saphenous vein strip. EC_{50} represents the concentration of compound which causes 50% of the maximum contraction effected by it.

TABLE

EXAMPLE	EC_{50}(M)	PERCENTAGE AGONISM RELATIVE TO 5-HT RESPONSE
3	3.78×10^{-9}	85
37	7.60×10^{-8}	72
46	1.60×10^{-7}	78
53	2.60×10^{-8}	75
60	9.20×10^{-9}	105
64	2.50×10^{-8}	79
66	1.90×10^{-8}	80

5-(5-Methoxycarbonyl-2-furyl)-3-(1-methylpyrrolidin-2(R)-ylmethyl)-1H-indole (see Example 65) was reacted with lithium aluminium hydride, in tetrahydrofuran, using a procedure similar to that described in Example 63. This gave the title compound. Found: C,70.59; H,6.81; N,8.41. $C_{19}H_{22}N_2O_2.3/16CH_2Cl_2$ requires: C,70.62; H,6.91; N,8.59%. ^{1}H-N.M.R. ($CDCl_3$): δ = 1.50-2.10(m,4H), 2.18-2.32(m,1H), 2.50(s,3H), 2.50-2.55 (m,1H), 2.60-2.80(m,1H), 3.10-3.30(m,2H), 4.80(s,2H), 5.30(s,3/8H), 6.40(d,1H), 6.50(d,1H), 7.02(s,1H), 7.32(d,1H), 7.50(d,1H), 7.90(s,1H), 8.02(bs,1H).

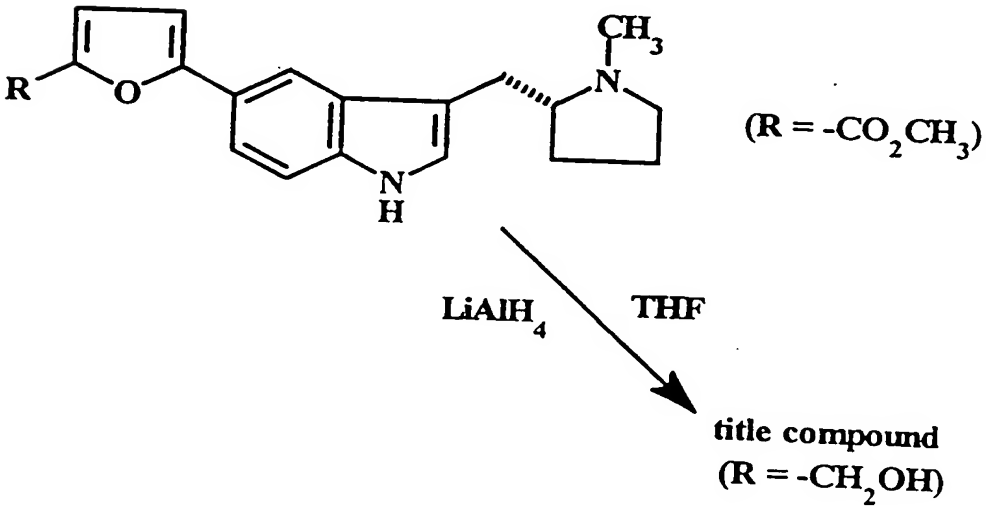
5-(5-Methoxycarbonyl-2-furyl)-3-(1-methylpyrrolidin-2(R)-ylmethyl)-1-triisopropylsilylindole (see Preparation 62) was reacted with tetra-n-butylammonium fluoride in tetrahydrofuran, using a procedure similar to that described in Example 62. This gave the title compound as a foam. Found: C,70.74; H,6.52; N,8.47. $C_{20}H_{22}N_2O_3$ requires: C,70.98; H,6.52; N,8.28%.

^{1}H-N.M.R. ($CDCl_3$): δ = 1.45-1.90(m,4H), 2.15-2.25(m,1H), 2.50(s,3H), 2.45-2.70(m,2H), 3.10-3.25(m,2H), 3.92(s,3H), 6.70(d,1H), 7.10(s,1H), 7.18-7.25(m, integral obscured by solvent), 7.40(d,1H), 7.62(d,1H), 8.00(s,1H), 8.10(bs,1H).

EXAMPLE 66

This Example illustrates the preparation of:

5-(5-Hydroxymethyl-2-furyl)-3-(1-methylpyrrolidin-2(R)-ylmethyl)-1H-indole



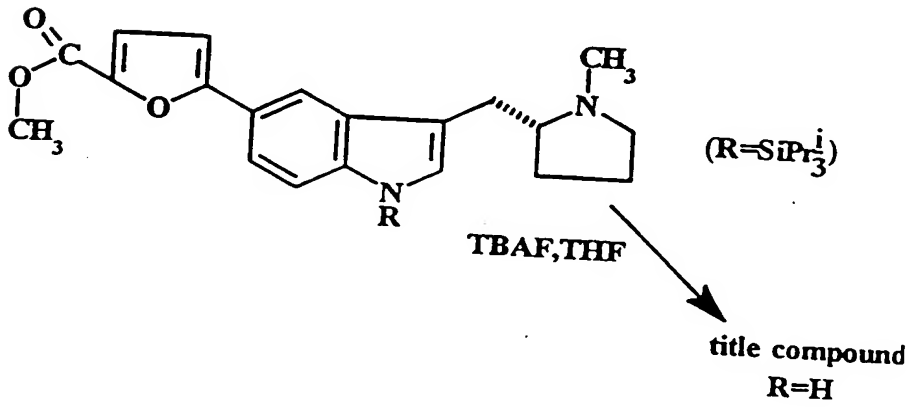
5-(5-Carbamoyl-2-thienyl)-3-(1-methylpyrrolidin-2(R)-ylmethyl)-1-triisopropylsilylindole (see Preparation 61) was reacted with tetra-n-butylammonium fluoride in tetrahydrofuran, using a procedure similar to that described in Example 62. This yielded the title compound as an off-white foam. Found: C,64.93; H,6.33; N,11.60. $C_{19}H_{21}N_3OS.3/16CH_2Cl_2$ requires: C,64.84; H,6.06; N,11.82%.

^{1}H-N.M.R. (D_6-DMSO): δ = 1.40-1.80(m,4H), 2.05-2.20(m,1H), 2.35(s,3H), 2.40-2.70(m, integral obscured by solvent), 2.90-3.15(m,2H), 5.75(s,3/8H), 7.15(s,1H), 7.25-7.40(m,4H), 7.70(d,1H), 7.80(s,1H), 7.90(bs,1H), 10.95(bs,1H).

EXAMPLE 65

This Example illustrates the preparation of:

5-(5-Methoxycarbonyl-2-furyl)-3-(1-methylpyrrolidin-2(R)-ylmethyl)-1H-indole



the aqueous phase extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with dichloromethane/methanol/ammonium hydroxide (90:10:0.7), to afford, after combination and evaporation of the appropriate fractions, the title compound as a white foam (298mg). Found: C,71.55; H,6.93; N,12.20. $C_{20}H_{22}N_3O.1/5CH_2Cl_2$ requires: C,71.70; H,6.97; N,12.42%.

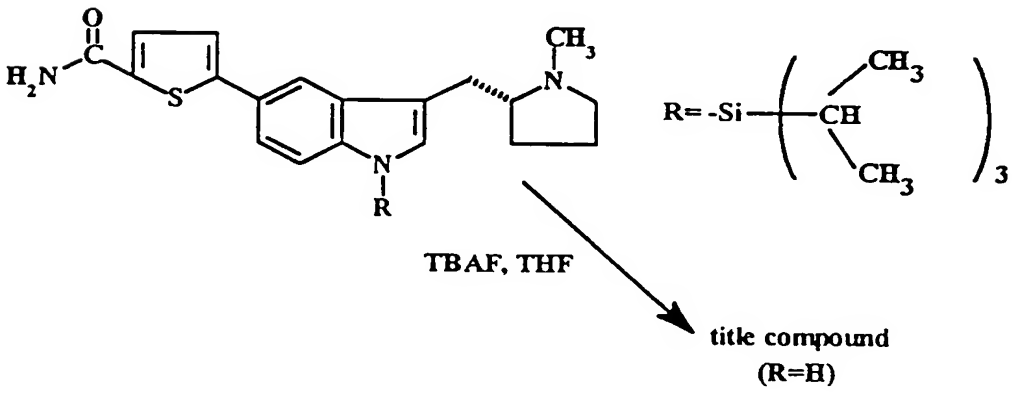
$[\alpha]_D^{25}$ +51° (c=0.1 in MeOH).

^{1}H-N.M.R. ($CDCl_3$): δ = 1.55-2.00(m,4H), 2.40-2.80(m,1H), 2.50(s,3H), 2.50-2.70(m,1H), 2.70-2.85(m,1H), 3.18-3.35(m,2H), 4.82(s,2H), 5.25(s,2/5H), 7.05-7.12(m,2H), 7.45(d,1H), 7.62-7.80(m,2H), 7.88(d,1H), 8.20-8.30(m,2H).

EXAMPLE 64

This Example illustrates the preparation of:

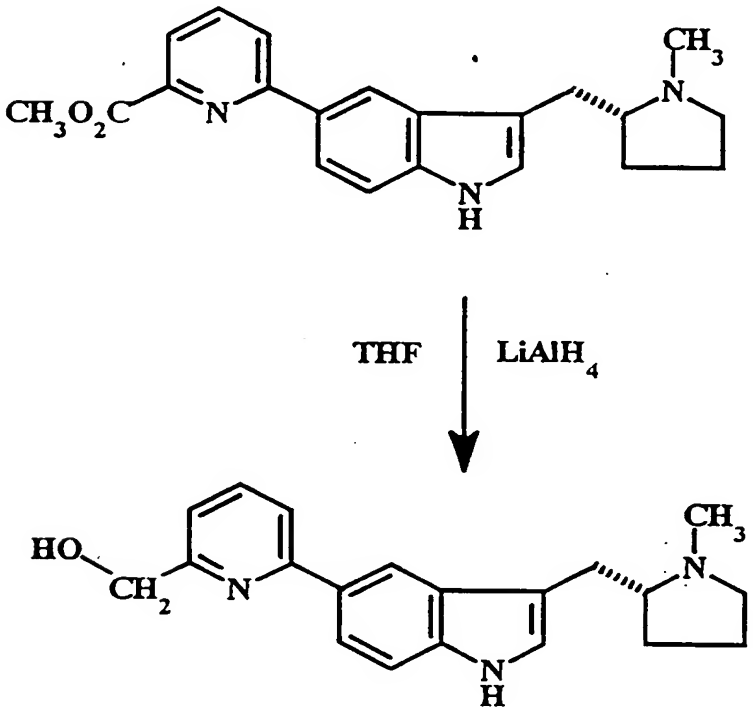
5-(5-Carbamoyl-2-thienyl)-3-(1-methylpyrrolidin-2(R)-ylmethyl)-1H-indole



EXAMPLE 63

This Example illustrates the preparation of:

5-(6-Hydroxymethyl-2-pyridyl)-3-(1-methylpyrrolidin-2(R)-ylmethyl)-1H-indole



(title compound)

A solution of 5-(3-Methoxycarbonyl-2-pyridyl)-3-(1-methylpyrrolidin-2(R)-ylmethyl)-1H-indole (393mg, 1.073mmol) (see Example 62) in tetrahydrofuran (2.5ml) was added dropwise, with stirring, to a flask containing a solution of lithium aluminium hydride in tetrahydrofuran (35.9mg of $LiAlH_4$ in 10.0ml THF) under a nitrogen atmosphere. The reaction was stirred for 24 hours whereupon the reaction mixture was quenched with aqueous sodium carbonate and

A solution of tetra-n-butylammonium fluoride (n-Bu_4NF) in tetrahydrofuran (1.15ml, 1M solution, 1.15mmol) was added in one portion to a solution of 5-(3-methoxycarbonyl-2-pyridyl)-3-(1-methylpyrrolidin-2(R)-ylmethyl)-1-triisopropylsilylindole (370mg, 0.730mmol) (see Preparation 60) in tetrahydrofuran (3.0ml), under nitrogen. The reaction was halted after 15 minutes and the solvent removed under reduced pressure. The residue was dissolved in ethyl acetate and the resultant solution washed with aqueous sodium carbonate. The organic layer was dried (Na_2SO_4) and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel to afford, after combination of the appropriate fractions, the title compound (200mg) as a clear oil. Found: C,70.64; H,6.99; N,11.72. $C_{21}H_{23}N_3O_2.\frac{1}{2}H_2O$ requires: C,70.36; H,6.75; N,11.72%.

^{1}H-N.M.R. ($CDCl_3$): δ = 1.50-1.95(m,5H), 2.12-2.25(m,1H), 2.45-2.60(m,1H), 2.50(s,3H), 2.60-2.80(m,1H), 3.10-3.20(m,1H), 3.20-3.35(m,1H), 4.05(s,3H), 7.05(s,1H), 7.45(d,1H), 7.85-8.02(m,4H), 8.10(ms,1H), 8.30(s,1H).

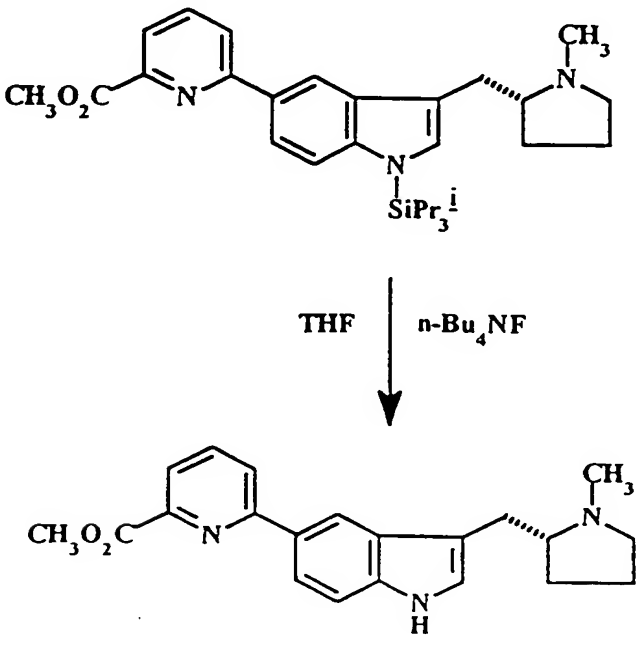
5-Carbamoyl-3-pyridyltri-n-butylstannane (see Preparation 43) and 5-bromo-3-(1-cyclopropylmethylpyrrolidin-2(R)-ylmethyl)-1H-indole (see Preparation 56) were reacted together in the presence of palladium (II) acetate, tri-o-tolylphosphine and triethylamine using a procedure similar to that described in Example 1. This yielded the title compound. Found: C,71.56; H,7.13; N,13.72. $C_{23}H_{26}N_4O.3/16CH_2Cl_2$ requires: C,71.33; H,6.81; N,14.35%.

^{1}H-N.M.R. (D_6-DMSO): δ = 0.10-0.20(m,2H), 0.35-0.55(m,2H), 0.80-0.95(m,1H), 1.40-1.75(m,4H), 1.90-2.05(m,1H), 2.05-2.25(m,1H), 2.40-2.60(m, integral obscured by solvent), 2.80-2.90(m,1H), 3.05-3.15(m,1H), 3.15-3.50(m, integral obscured by solvent), 5.70(s,3/8H), 7.20(s,1H), 7.40-7.42(m,2H), 7.60(bs,1H), 7.87(s,1H), 8.25(bs,1H), 8.40(m,1H), 8.90(d,1H), 9.00(d,1H).

EXAMPLE 62

This Example illustrates the preparation of:

5-(6-Methoxycarbonyl-2-pyridyl)-3-(1-methylpyrrolidin-2(R)-ylmethyl)-1H-indole



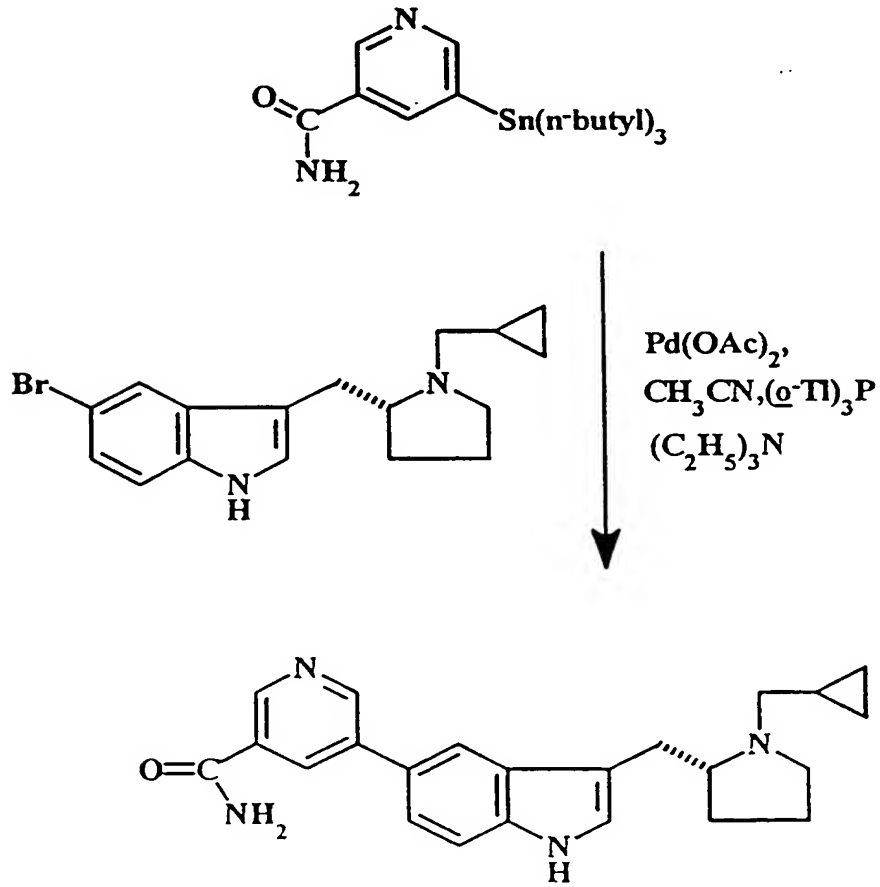
(title compound)

[$(C_2H_5)_3N$] using a procedure similar to that described in Example 1. This yielded the title compound. Found: C,73.72; H,7.53; N,15.84; $C_{21}H_{24}N_4.1/8CH_2Cl_2.1/8H_2O$ requires: C,73.47; H,7.15; N,16.23%. ^{1}H-N.M.R. ($CDCl_3$): δ = 0.10-0.20(m,2H), 0.40-0.60(m,2H), 0.90-1.05(m,1H), 1.40-1.90(m,4¼H), 2.00-2.15(m,1H), 2.20-2.40(m,1H), 2.65-3.10(m,2H), 2.90-3.00(m,1H), 3.15-3.30(m,1H), 3.40-3.55(m,1H), 5.25(s,¼1H), 7.15(bs,1H), 7.37(d,1H), 7.45(d,1H), 7.68(s,1H), 8.20(bs,1H), 9.00(s,2H), 9.10(s,1H).

EXAMPLE 61

This Example illustrates the preparation of:

5-(5-Carbamoyl-3-pyridyl)-3-(1-cyclopropyl-methylpyrrolidin-2(R)-ylmethyl)-1H-indole



(title compound)

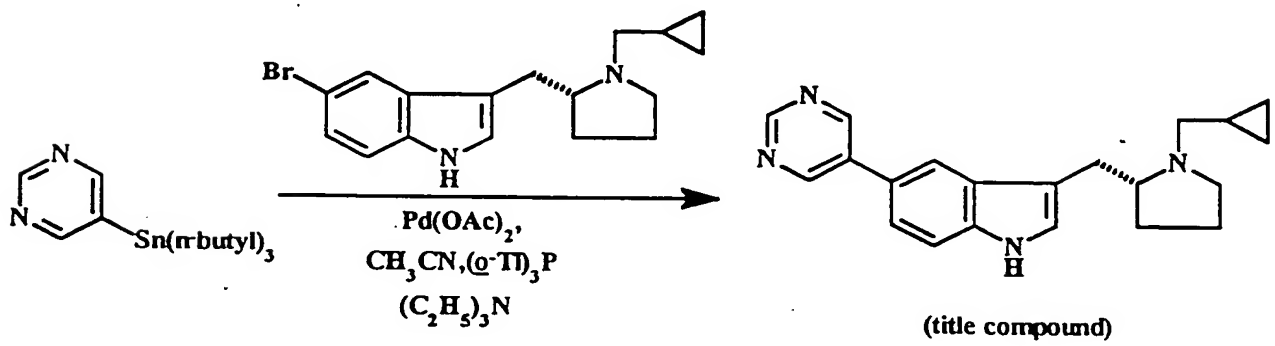
1-(t-butoxycarbonyl)-5-(6-N,N-dimethylcarbamoyl-2-pyridyl)-3-(1-methylpyrrolidin-2(R)-ylmethyl)-indole (see Preparation 54) was reacted with trifluoroacetic acid using a procedure similar to that described in Example 58. This yielded the title compound. Found: C,70.91%; H,7.36; N,14.47; $C_{22}H_{26}N_4O.1/8CH_3CH_2O_2CCH_3.½H_2O$ requires: C,70.65; H,7.38; N,14.65%.

^{1}H-N.M.R. (D_6-DMSO): δ = 1.15(t,3/8H), 1.35-1.75(m,5H), 1.95(s,3/8H), 2.35(s,3H), 2.20-2.65(m, integral obscured by solvent), 2.80-3.10(m,2H), 3.00(s,3H), 3.05(s,3H), 3.97(q,¼H), 7.17(s,1H), 7.30-7.50(m,2H), 7.77(d,1H), 7.90(dd,1H), 7.95(d,1H), 8.20(s,1H).

EXAMPLE 60

This Example illustrates the preparation of:

3-(1-Cyclopropylmethylpyrrolidin-2(R)-ylmethyl)-5-(5-pyrimidinyl)-1H-indole



(title compound)

(5-Pyrimidinyl)tri-n-butylstannane (see Preparation 45) and 5-bromo-3-(1-cyclopropylmethylpyrrolidin-2(R)-ylmethyl)-1H-indole (see Preparation 56) were reacted together in the presence of palladium (II) acetate [$Pd(OAc)_2$], tri-o-tolylphosphine [$(o\text{-}Tl)_3P$] and triethylamine

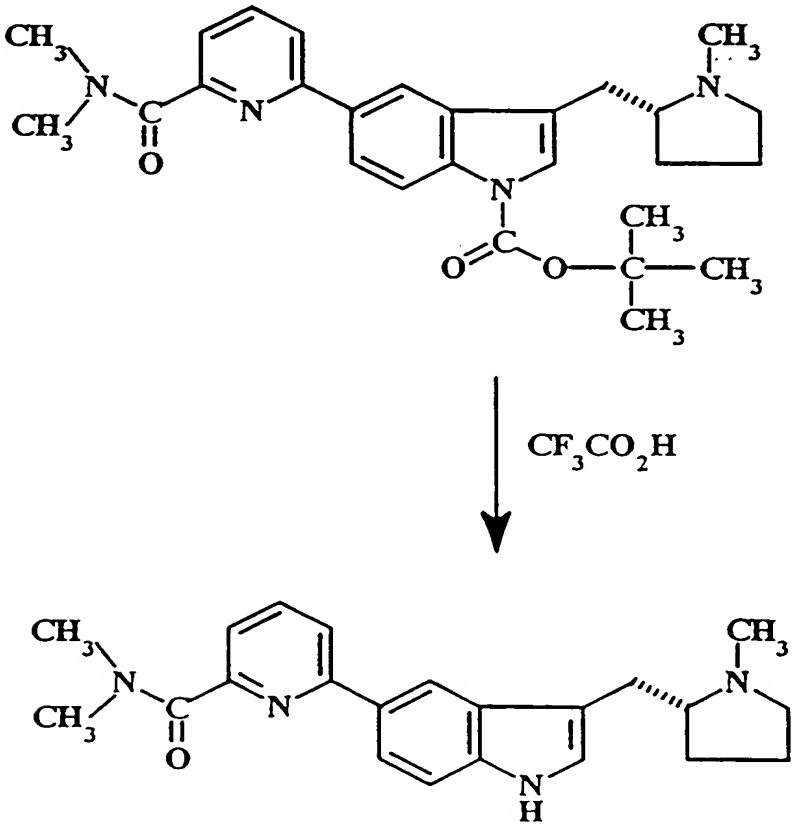
pressure gave the crude product. This was purified by column chromatography on silica gel to afford, after combination of the appropriate fractions, the title compound (30mg). Found: C,70.81; H,6.78; N,15.32; $C_{21}H_{24}N_4O.1/8CH_2Cl_2$ requires: C,70.66; H,6.81; N,15.61%.

^{1}H-N.M.R. ($CDCl_3$): δ = 1.50-1.95(m,4H), 2.20-2.35(m,1H), 2.47(s,3H), 2.45-2.65(m,1H), 2.65-2.75(m,1H), 3.07(s,s,3H), 3.10-3.30(m,2H), 5.30(s,¼H), 7.10(s,1H), 7.40-7.50(m,2H), 7.85(s,1H), 8.20(s,1H), 8.37(s,1H), 8.90(s,1H), 9.00(s,1H).

EXAMPLE 59

This Example illustrates the preparation of:

5-(6-N,N-dimethylcarbamoyl-2-pyridyl)-3-(1-methylpyrrolidin-2(R)-ylmethyl)-1H-indole

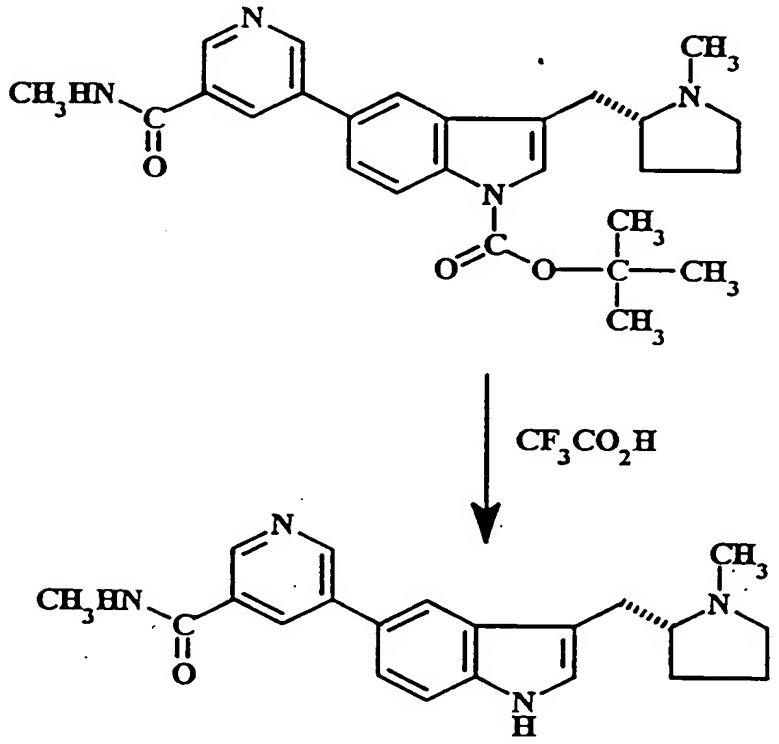


(title compound)

EXAMPLE 58

This Example illustrates the preparation of:

5-(5-(N-methylcarbamoyl)-3-pyridyl)-3-(1-methylpyrrolidin-2(R)-ylmethyl)-1H-indole



(title compound)

1-(t-Butoxycarbonyl)-5-(5-N-methycarbamoyl-3-pyridyl)-3-(1-methylpyrrolidin-2(R)-ylmethyl)-indole (88mg, 0.20mmol) (see Preparation 53) was dissolved in trifluoroacetic acid (2.0ml) and the reaction was stirred for ½ an hour at room temperature, followed by 1½ hours at reflux. The reaction was then cooled to room temperature and the trifluoroacetic acid removed by evaporation under reduced pressure followed by azetroping with dichloromethane. The residue was partitioned between ethyl acetate and aqueous sodium carbonate. The aqueous phase was extracted with ethyl acetate and the organic layers combined and dried (Na_2SO_4). Solvent removal under reduced

^{1}H-N.M.R. ($CDCl_3$): δ = 1.50-2.15(m,5.2H), 2.25-2.40(m,1H), 2.47(s,3H), 2.50-2.70(m,1H), 2.70-2.80(m,1H), 3.15-3.35(m,2H), 7.15(s,1H), 7.30-7.50(m,3H), 7.80(s,1H), 7.95(d,1H), 8.25(bs,1H), 8.55(d,1H), 8.90(s,1H).

EXAMPLE 57

This Example illustrates the preparation of:

3-(1-methylpyrrolidin-2(R)-ylmethyl)-5-(4-pyridyl)-1H-indole

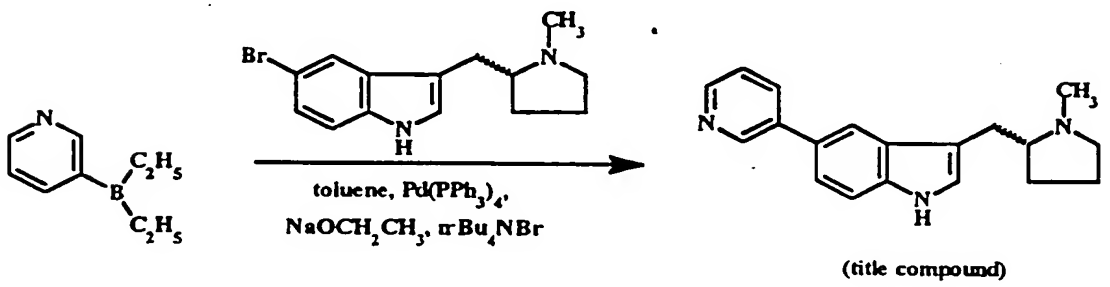
5-Bromo-3-(1-methylpyrrolidin-2(R)-ylmethyl)-1H-indole (see Preparation 36) and diethyl (4-pyridyl)borane (see Preparation 50) were reacted together in the presence of sodium ethoxide, n-butylammonium bromide and tetrakis(triphenylphosphine)palladium(O) using a procedure similar to that in Example 56. This gave the title compound. Found: C,75.77; H,7.16; N,13.78%; $C_{19}H_{21}N_3.1/8CH_2Cl_2$ requires: C,76.06; H,7.09; N,13.91%.

^{1}H-N.M.R. ($CDCl_3$): δ = 1.50-1.90(m,4H), 2.20-2.30(m,1H), 2.50(s,3H), 2.40-2.55(m,1H), 3.10-3.30(m,2H), 5.30(s,¼H), 7.10(s,1H), 7.45(d,1H), 7.50(d,1H), 7.60(d,2H), 7.90(s,1H), 8.25(bs,1H), 8.65(d,2H).

EXAMPLE 56

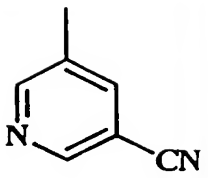
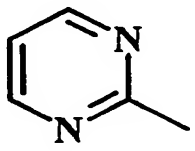
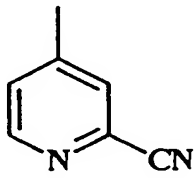
This Example illustrates the preparation of:

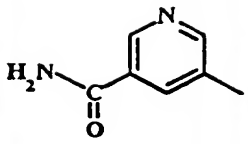
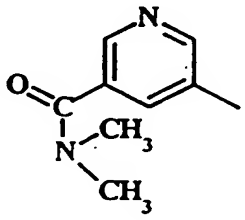
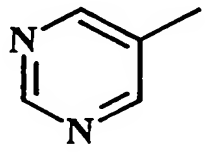
3-(1-methylpyrrolidin-2(R)-ylmethyl)-5-(3-pyridyl)-1H-indole



(title compound)

To a stirred solution of 5-bromo-3-(1-methylpyrrolidin-2(R)-ylmethyl)-1H-indole (847mg, 2.89mmol) (see Preparation 36) and tetrakis(triphenylphosphine)palladium(O) (116mg, 0.10mmol) in toluene (10ml) under N_2 was added sequentially at room temperature tetra n-butylammonium bromide (64mg, mmol), ethanolic sodium ethoxide (0.514g, 7.55mmol of sodium ethoxide in 2.8ml of ethanol) and diethyl(3-pyridyl)borane (0.294g, 2.00mmol) (see Preparation 49). The reaction was refluxed for 2 hours, cooled to room temperature, diluted with ethyl acetate and washed with a 1:1 mixture of aqueous sodium carbonate and brine. The organic layer was dried (Na_2SO_4) and the solvent removed under reduced pressure to give the crude product. This was purified by column chromatography on silica gel, eluting with dichloromethane/methanol/ammonium hydroxide (89:10:1) to afford, after combination of the appropriate fractions, the title compound (300mg). Found: C,75.92; H,7.36; N,13.52; $C_{19}H_{21}N_3.3/5H_2O$ requires: C,75.52; H,7.40; N,13.91%.

Ex No	R	Analysis (%)	^{1}H-NMR (in $CDCl_3$ unless otherwise stated)
53		Found: C,74.06; H,5.99; N,16.38; $C_{20}H_{20}N_4.3/8CH_2Cl_2$ requires: C,73.64; H,6.29; N,16.86%.	δ = 1.50-1.90 (m,4H), 2.20-2.30(m,1H), 2.50(s,3H), 2.40-2.55(m,1H), 2.60-2.75(m,1H), 3.10-3.30(m,2H), 5.30 (s,3/4H), 7.10(s,1H), 7.35(d,1H), 7.50 (d,1H), 7.75(s,1H), 8.15(s,s,2H), 8.80 (s,1H), 9.10(s,1H).
54		Found: C,71.16; H,6.56; N,17.20; $C_{18}H_{20}N_4.3/16CH_2Cl_2$ requires: C,70.85; H,6.66; N,18.17%.	δ = 1.55-1.95(m,4H), 2.20-2.30(m,1H), 2.50 (s,3H), 2.50-2.80 (m,2H), 3.10-3.35 (m,2H), 5.30(s,3/8H), 7.10(d,1H), 7.15 (s,1H), 7.05(d,1H), 8.10(s,1H), 8.30 (dd,1H), 8.75(s,1H), 8.80(d,2H).
55		Found: C,69.01; H,5.78; N,15.48; $C_{20}H_{20}N_4.1/3CH_2Cl_2$.½H_2O requires: C,69.04; H,6.17; N,15.84.	δ = 1.45-1.90(m,5H), 2.15-2.35(m,1H), 2.45(s,3H), 2.35-2.60(m,1H), 2.60-2.75(m,1H), 3.10-3.30(m,2H), 5.30 (s,2/3H), 7.15(s,1H), 7.40-7.55(m,2H), 7.75(d,1H), 7.85 (s,1H), 7.95(s,1H), 8.20(bs,1H), 8.70 (d,1H).

Ex No	R	Analysis (%)	^{1}H-NMR (in $CDCl_3$ unless otherwise stated)
50		Found: C,70.74; H,6.30; N,16.08; $C_{20}H_{22}N_4O.1/10$ CH_2Cl_2 requires: C,70.41; H,6.53; N,16.34%.	(D_6-DMSO): δ = 1.35-1.75(m,4H), 2.00-2.10(m,1H), 2.30(s,3H), 2.25-2.60(m, integral obscured by solvent), 2.90-3.00 (m,1H), 3.05-3.15 (m,1H), 5.70 (s,1/5H), 7.20 (s,1H), 7.40-7.45 (s,2H), 7.60 (bs,1H), 7.90 (s,1H), 8.20 (bs,1H), 8.40 (s,1H), 8.90(s,1H), 9.00(s,1H).
51		Found: C,70.67; H,7.33; N,14.45; $C_{22}H_{26}N_4O.3/16$ CH_2Cl_2 requires: C,70.42; H,7.03; N,14.81%.	δ = 1.50-1.90(m,4H), 2.20-2.35(m,1H), 2.50(s,3H), 2.40-2.60(m,1H), 2.65-2.75(m,1H), 3.05-3.30(m,8H), 5.30(s,3/8H), 7.10(s,1H), 7.40(d,1H), 7.45(d,1H), 7.80(s,1H), 8.00(s,1H), 8.20(s,1H), 8.60(s,1H), 8.95(s,1H).
52		Found: C,73.77; H,6.84; N,18.62; $C_{18}H_{20}N_4.1/8H_2O$ requires: C,73.38; H,6.93; N,19.02%.	δ = 1.50-1.90(m,4H), 2.20-2.30(m,1H), 2.50(s,3H), 2.40-2.55(m,1H), 2.65-2.75(m,1H), 3.10-3.30(m,2H), 7.10(s,1H), 7.40(d,1H), 7.50(d,1H), 7.80(s,1H), 8.60(bs,1H), 9.00(s,2H), 9.20(s,1H).

3-(1-Methylpyrrolidin-2(R)-ylmethyl)-5-(5-methoxycarbonyl-2-pyridyl)-1H-indole (50mg, 0.143mmol) (see Example 48) in tetrahydrofuran (0.7ml) was added to a solution composed of lithium aluminium hydride in tetrahydrofuran (0.12ml of a 1M solution) and tetrahydrofuran (0.3ml) under nitrogen. The reaction was stirred for 1 hour at room temperature whereupon the reaction mixture was partitioned between aqueous sodium carbonate and ethyl acetate. The aqueous phase was extracted with ethyl acetate and the combined organic phases dried (Na_2SO_4). Evaporation of the solvent gave the crude product. This was purified by column chromatography on silica gel, eluting with dichloromethane/methanol/ammonium hydroxide (89:10:1) to afford, after combination of the appropriate fractions, the title compound (21mg, 0.065mmol).

LRMS, m/z = 322 [MH+).

^{1}H-N.M.R. (D_6-DMSO): δ = 1.50-1.90, 2.20-2.60(m, integral obscured by solvent), 4.60(s,s,2H), 5.35(bs,1H), 7.25(s,1H), 7.35(d,1H), 7.45(d,1H), 7.80(s,1H), 7.95(s,1H), 8.40(s,1H), 8.75(s,1H).

EXAMPLES 50 to 55

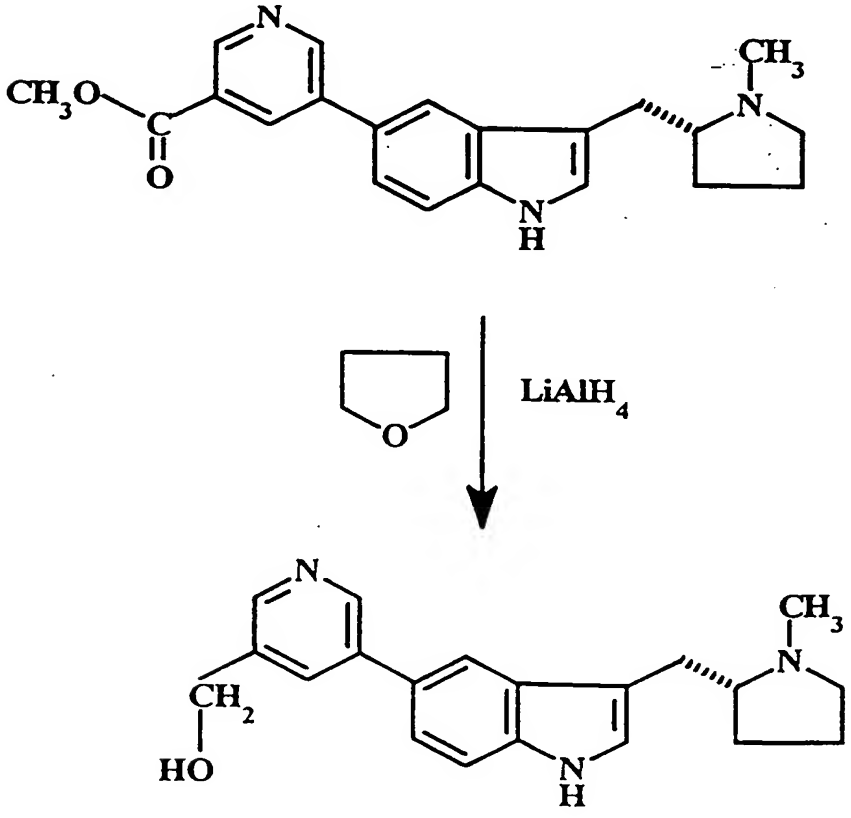
The following examples were prepared from the appropriate stannane and 5-bromo-3-(1-methylpyrrolidin-2(R)-ylmethyl)-1H-indole (see Preparation 36) using a procedure similar to that described in Example 1.

5-Methoxycarbonyl-3-pyridyltri-n-butylstannane (see Preparation 42) and 5-bromo-3-(1-methylpyrrolidin-2(R)-ylmethyl)-1H-indole (see Preparation 36) were reacted together in the presence of tri-o-tolylphosphine, triethylamine and palladium (II) acetate using a procedure similar to that described in Example 1. This yielded the title compound as an oil. The product, which was impure, was used without characterisation in the preparation of Example 49.

EXAMPLE 49

This Example illustrates the preparation of:

5-(5-Hydroxymethyl-3-pyridyl)-3-(1-methylpyrrolidin-2(R)-ylmethyl)-1H-indole



(title compound)

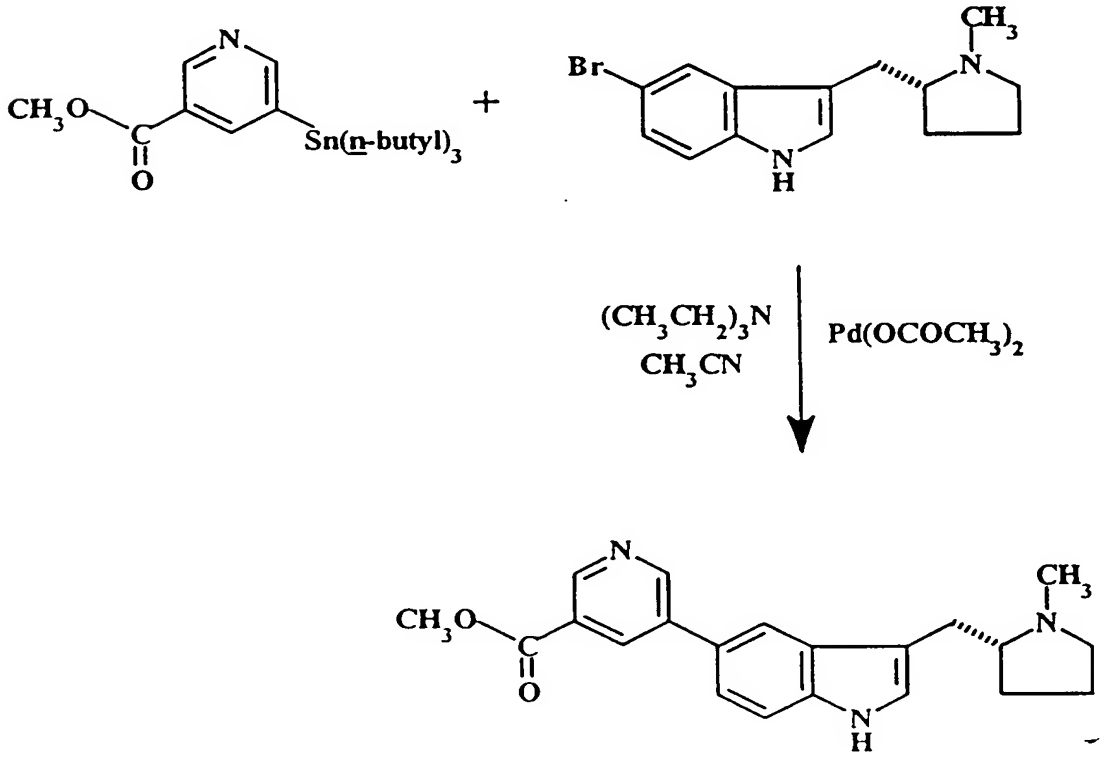
2-Pyridyltri-n-butylstannane and 5-bromo-3-(1-methylpyrrolidin-2(R)-ylmethyl)-1H-indole (see Preparation 36) were reacted together in the presence of tri-o-tolylphosphine, triethylamine and palladium (II) acetate using a procedure similar to that described in Example 1. This yielded the title compound. Found: C,75.37; H,6.93; N,13.66; $C_{19}H_{21}N_3.1/6CH_2Cl_2$ requires: C,75.34; H,7.04; N,13.75%.

^{1}H-N.M.R. ($CDCl_3$): δ = 1.50-1.95(m,4H), 2.20-2.30(m,1H), 2.45(s,3H), 2.45-2.65(m,1H), 2.65-2.75(m,1H), 3.10-3.25(m,1H), 3.25-3.30(m,1H), 5.25(s,1/3H), 7.10(s,1H), 7.20(m,1H), 7.45(d,1H), 7.70(d,1H), 7.75(d,1H), 7.85(dd,1H), 8.10(bs,1H), 8.20(s,1H), 8.70(d,1H).

EXAMPLE 48

This Example illustrates the preparation of:

3-(1-Methylpyrrolidin-2(R)-ylmethyl)-5-(5-methoxycarbonyl-3-pyridyl)-1H-indole



EXAMPLE 46

This Example illustrates the preparation of:

3-[1-(2-N,N-dimethylcarbamoylethyl)pyrrolidin-2(R)-ylmethyl]-5-(3-N,N-dimethylcarbamoylphenyl)-1H-indole

5-(3-N,N-dimethylcarbamoylphenyl)-3-(pyrrolidin-2(R)-ylmethyl)-1H-indole (100mg,0.256mmol) (see Example 35) and N,N-dimethylacrylamide were reacted together in 1,2-dimethoxyethane, in the presence of triethylamine, using a procedure similar to that described in Example 43. This yielded the title compound as a white foam (78mg). Found: C,66.19; H,7.31; N,11.23; $C_{27}H_{34}N_4O_2.2/3CH_2Cl_2$ requires: C,66.04; H,7.14; N,11.13%.

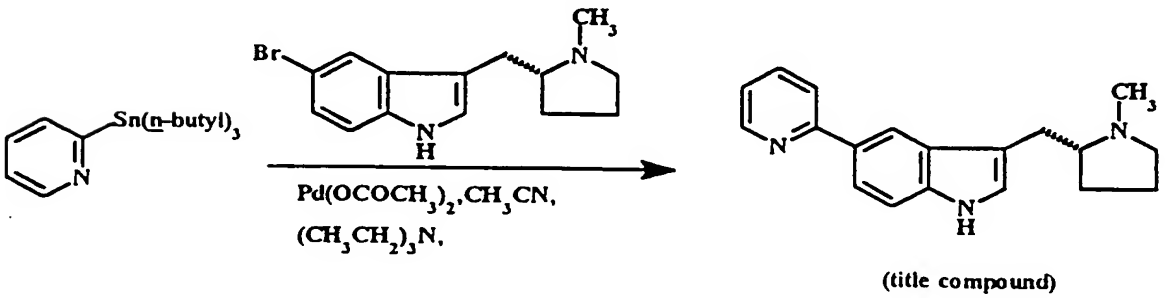
$[\alpha]_D^{25}$ +5° (c=0.1 in methanol).

^{1}H-N.M.R. ($CDCl_3$): δ = 1.50-1.90(m,4H), 2.30-2.50(m,1H), 2.55-3.10(m,18H), 3.15-3.40(m,2H), 5.25(s,1 1/3H), 7.05(s,1H), 7.25(d,1H), 7.30-7.45(m,3H), 7.60-7.65(m,2H), 7.70(s,1H), 8.50(s,1H).

EXAMPLE 47

This Example illustrates the preparation of:

3-(1-methylpyrrolidin-2(R)-ylmethyl)-5-(2-pyridyl)-1H-indole



(title compound)

EXAMPLE 44

This Example illustrates the preparation of:

3-[1-(2-Carbamoylethyl)pyrrolidin-2(R)-ylmethyl]-5-(3-carbamoylphenyl)-1H-indole

5-(3-carbamoyl)-3-(pyrrolidin-2(R)-ylmethyl)-1H-indole (52mg, 0.155mmol) (see Example 38) and acrylamide were reacted together in 1,2-dimethoxyethane, in the presence of triethylamine, using a procedure similar to that described in Example 43. This yielded the title compound as a white solid (38mg). Found: C,66.01; H,6.77; N,12.91; $C_{23}H_{26}N_4O_2.1/3CH_2Cl_2.1/3H_2O$ requires: C,65.97; H,6.49; N,13.19%. $[\alpha]_D^{25}$ +45° (c=0.1 in methanol).

^{1}H-N.M.R. ($CDCl_3/CD_3OD$): δ = 1.60-1.95(4H), 2.25-3.00(m,6H), 3.15-3.40(m, integral obscured by solvent), 5.30(s,2/3H), 7.05(s,1H), 7.35-7.45(m,2H), 7.50(dd,1H), 7.75-7.90(m,2H), 7.90(s,1H), 8.15(s,1H).

EXAMPLE 45

This Example illustrates the preparation of:

3-[1-(2-Carbamoylethyl)pyrrolidin-2(R)-ylmethyl]-5-(4-carbamoylphenyl)-1H-indole

5-(4-carbamoylphenyl)-3-(pyrrolidin-2(R)-ylmethyl)-1H-indole (60mg, 0.180mmol) (see Example 39) and acrylamide were reacted together in 1,2-dimethoxyethane, in the presence of triethylamine, using a procedure similar to that described in Example 43. This yielded the title compound as a white solid (42mg). Found: C,64.48; H,6.98; N,12.47; $C_{23}H_{26}N_4O_2.2H_2O.1/3CH_3OH$ requires: C,64.10; H,7.22; N,12.82%.

^{1}H-N.M.R. ($CDCl_3/CD_3OD$): δ = 1.50-1.90(m,4H), 2.15-2.55(m,4H), 2.57-2.70(m,1H), 2.70-2.85(m,1H), 3.10-3.30(m,3H), 3.30(s,1H), 7.00(s,1H), 7.30-7.40(m,2H), 7.65(d,2H), 7.70(s,1H), 7.80(d,2H).

To a stirred solution of 5-(3-N,N-dimethycarbamoylphenyl)-3-(pyrrolidin-2(R)-ylmethyl)-1H-indole (131mg, 0.336mmol) (see Example 35) in 1,2-dimethoxyethane (2.6ml) was added triethylamine (0.13ml, mmol) and acrylamide (26mg, 0.369mmol). The mixture was stirred at reflux, under nitrogen, for 18 hours. The reaction was then cooled to room temperature and partitioned between ethyl acetate (100ml) and water (100ml). The organic phase was separated, washed with water (100ml) and dried (sodium sulphate). Solvent removal under reduced pressure gave the crude product. Purification by column chromatography on silica gel, eluting with dichloromethane/ methanol/ammonium hydroxide (90:10:0.5) afforded, after combination and evaporation of the appropriate fractions, the title compound as a white foam (80mg).
Found: C,63.85; H,6.78; N,11.84; $C_{25}H_{30}N_4O_2.3/4CH_2Cl_2$ requires: C,64.14; H,6.58; N,11.62%.
$[\alpha]_D^{25}$ +54° (c=0.1 in methanol).

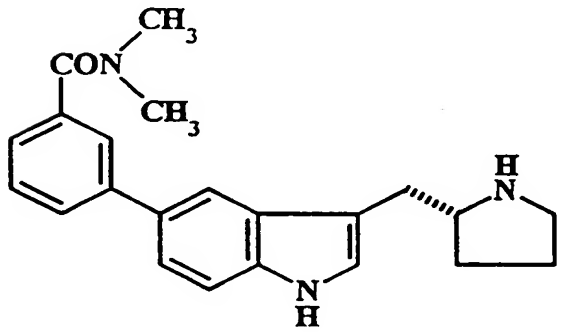
^{1}H-N.M.R. ($CDCl_3$): δ = 1.50-1.95(m,4H), 2.15-2.60(m,5H), 2.65-2.80(m,1H), 2.80-2.95(m,1H), 3.00(s,3H), 3.15(s,3H), 3.15-3.35(m,2H), 5.30(s,1½H), 5.50(bs,1H), 7.00(s,1H), 7.25-7.50(m,4H), 7.65(d,1H), 7.70(s,1H), 7.75(s,1H), 8.10(bs,1H), 8.50(s,1H).

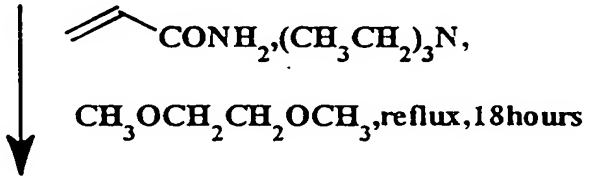
^{1}H-N.M.R. ($CDCl_3/CD_3OD$): δ = 1.45-1.85(m,4H), 2.20-2.35(m,1H), 2.40-2.55(m,1H), 2.55-2.70(m,1H), 2.70-2.90(m,1H), 3.10-3.30(m,3H), 3.25(s,3H), 3.50(t,2H), 5.25(s,1H), 7.00(s,1H), 7.30-7.35(m,2H), 7.60(d,2H), 7.70(s,1H), 7.80(d,2H).

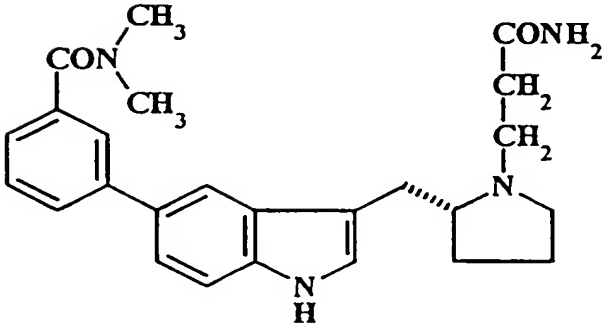
EXAMPLE 43

This Example illustrates the preparation of:

3-[1-(2-Carbamoylethyl)pyrrolidin-2(R)-ylmethyl]-5-(3-N,N-Dimethylcarbamoylphenyl)-1H-indole







(title compound)

EXAMPLE 41

This Example illustrates the preparation of:

5-(3-Carbamoylphenyl)-3-[1-(2-methoxyethyl)-pyrrolidin-2(R)-ylmethyl]-1H-indole

5-(3-Carbamoylphenyl)-3-(pyrrolidin-2(R)-ylmethyl)-1H-indole (60mg, 0.1881mmol) (see Example 38) and 2-bromomethoxyethane were reacted together in 1,2-dimethoxyethane, in the presence of sodium carbonate and sodium iodide using a procedure similar to that described in Example 40. This yielded the title compound as a white foam (48mg). Found: C,69.82; H,7.33; N,10.23; $C_{23}H_{27}N_3O_2.1/8CH_2Cl_2.\frac{1}{2}H_2O$ requires: C,69.94; H,7.17; N,10.58%.

$[\alpha]_D^{25}$ +38° (c=0.1 in methanol).

^{1}H-N.M.R. ($CDCl_3$): δ = 1.25(s,1H), 1.55-1.95(m,4H), 2.15-2.35(m,1H), 2.40-2.55(m,1H), 2.65-2.90(m,2H), 3.15-3.35(m,3H), 3.35(s,3H), 3.50-3.65(m,2H), 5.25(s,¼H), 5.65(bs,1H), 6.30(bs,1H), 7.05(s,1H), 7.35-7.55(m,3H), 7.70(d,1H), 7.80(d,1H), 7.85(s,1H), 8.10(bs,2H).

EXAMPLE 42

This Example illustrates the preparation of:

5-(4-Carbamoylphenyl)-3-[1-(2-methoxyethyl)-pyrrolidin-2(R)-ylmethyl]-1H-indole

5-(4-Carbamoylphenyl)-3-(pyrrolidin-2(R)-ylmethyl)-1H-indole (60mg, 0.1881mmol) (see Example 39) and 2-bromomethoxyethane were reacted together in 1,2-dimethoxyethane, in the presence of sodium carbonate and sodium iodide using a procedure similar to that described in Example 40. This yielded the title compound as a white foam (38mg). Found: C,65.45; H,7.21; N,9.58; $C_{23}H_{27}N_3O_2.\frac{1}{2}CH_2Cl_2.5/8H_2O$ requires: C,65.46; H,6.84; N,9.74%.

$[\alpha]_D^{25}$ +54° (c=0.1 in methanol).

To a stirred solution of 5-(3-N,N-Dimethylcarbamoylphenyl)-3-(pyrrolidin-2(R)-ylmethyl)-1H-indole (100mg, 0.2565mmol) (see Example 35) in 1,2-dimethoxyethane (2.0ml) was added sequentially sodium carbonate (27mg, 0.25mmol), sodium iodide (43mg, 0.29mmol) and finally 2-bromomethoxyethane (24μL, 36mg, 0.259mmol). The mixture was stirred at reflux under nitrogen, for 14 hours. The reaction was then cooled to room temperature and partitioned between ethyl acetate (200ml) and aqueous sodium carbonate (200ml). The organic layer was dried (sodium sulphate) and the solvent removed under reduced pressure to give the crude product. Purification by column chromatography on silica gel, eluting with dichloromethane/ methanol/ammonium hydroxide (90:10:0.1) afforded, after combination and evaporation of the appropriate fractions, the title compound as a white foam (63mg).
Found: C,66.46; H,7.28; N,9.30; $C_{25}H_{31}N_3O_2.2/3CH_2Cl_2$ requires: C,66.70; H,7.05; N,9.09%.
$[\alpha]_D^{25}$ +16° (c=0.1 in methanol).

^{1}H-N.M.R. ($CDCl_3$): δ = 1.65-2.05(m,4H), 2.60-2.80(m,2H), 2.85-3.45(m,4H), 2.90(s,3H), 3.10(s,3H), 3.30(s,3H), 3.40-3.70(m,3H), 5.25(s,1 1/3H), 7.25(s,1H), 7.20-7.40(m,4H), 7.60(d,1H), 7.65(s,1H), 7.20(s,1H), 8.70(s,1H).

3-(1-Benzyloxycarbonylpyrrolidin-2(R)-ylmethyl)-5-(4-carbamoylphenyl)-1H-indole (355mg, 0.784mmol) (see Preparation 41) in ethanol was reduced using catalytic hydrogenation, as described in Example 35. This gave the title compound as a white foam (210mg). Found: C,72.33; H,6.80; N,12.35; $C_{20}H_{21}N_3O.3/4H_2O$ requires: C,72.16; H,6.81; N,12.62%.

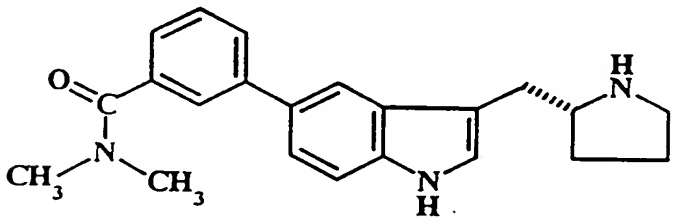
$[\alpha]_D^{25}$ -18° (c=0.1 in methanol).

^{1}H-N.M.R. ($CDCl_3/CD_3OD$): δ = 1.40-1.60(m,1H), 1.70-2.00(m,3H), 2.70-2.85(m,1H), 2.95-3.10(m,3H), 3.35-3.50(m,1H), 7.10(s,1H), 7.40-7.50(m,2H), 7.75(d,2H)m, 7.85(s,1H), 7.95(d,1H).

EXAMPLE 40

This Example illustrates the preparation of:

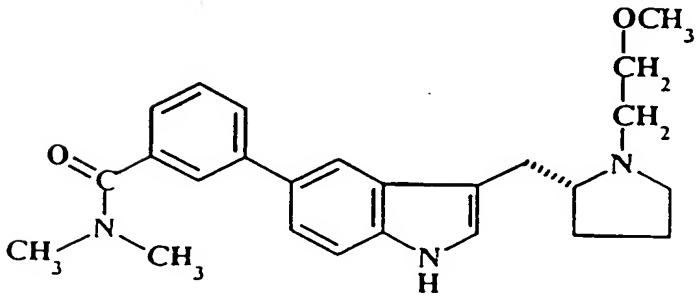
5-(3-N,N-Dimethylcarbamoylphenyl)-3-[1-(2-methoxyethyl)pyrrolidin-2(R)-ylmethyl]-1H-indole



(Example 35)

$BrCH_2CH_2OCH_3$;NaI;Na_2CO_3;

$CH_3OCH_2CH_2OCH_3$,reflux,14hours



(title compound)

3-(1-Benzyloxycarbonylpyrrolidin-2(R)-ylmethyl)-5-(3-carbamoylphenyl)-1H-indole (700mg, 1.391mmol) (see Preparation 40) in ethanol was reduced using catalytic hydrogenation, as described in Example 35. This gave the title compound as a white foam (345mg). Found: C,71.16; H,6.98; N,12.34; $C_{20}H_{21}N_3O.H_2O$ requires: C,71.19; H,6.87; N,12.45.

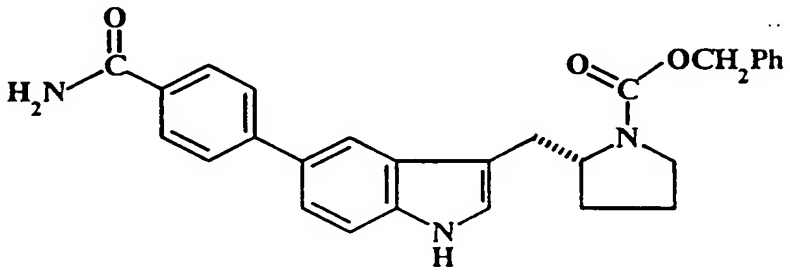
$[\alpha]_D^{25}$ -16° (c=0.1 in methanol).

^{1}H-N.M.R. ($CDCl_3/CD_3OD$): δ = 1.50-1.60(m,1H), 1.70-2.00(m,3H), 2.75-2.90(m,1H), 3.00-3.15(m,3H), 3.40-3.50(m,1H), 7.10(s,1H), 7.40(s,1H), 7.50(dd,1H), 7.75-7.85(m,2H), 7.90(s,1H), 8.15(s,1H).

EXAMPLE 39

This Example illustrates the preparation of:

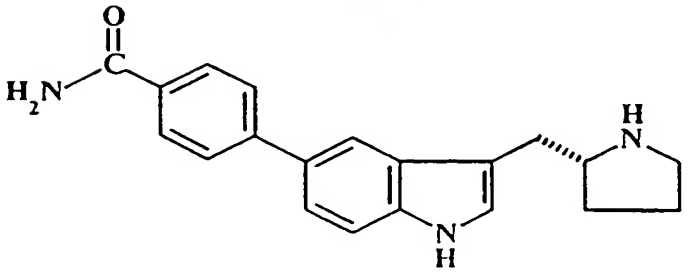
5-(4-Carbamoylphenyl)-3-(pyrrolidin-2(R)-ylmethyl)-1H-indole



(Preparation 41)

10% Pd/C, 1 bar H_2,

CH_3COCl, CH_3CH_2OH



(title compound)

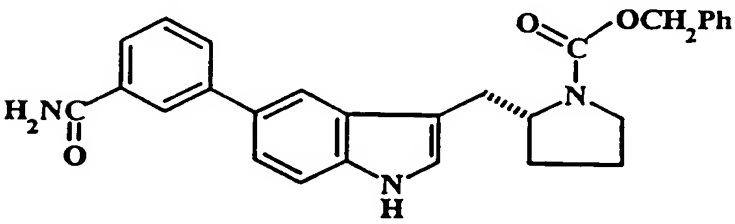
$[\alpha]_D^{25}$ -11° (c=0.1 in methanol).

^{1}H-N.M.R. (CD_3OD): δ = 1.40-1.60(m,1H), 1.60-2.00(m,3H), 2.70-3.05(m,3H), 3.25-3.50(m,2H), 4.60(s,2H), 7.10(s,1H), 7.30-7.45(m,6H), 7.60(d,2H), 7.80(s,1H).

EXAMPLE 38

This Example illustrates the preparation of:

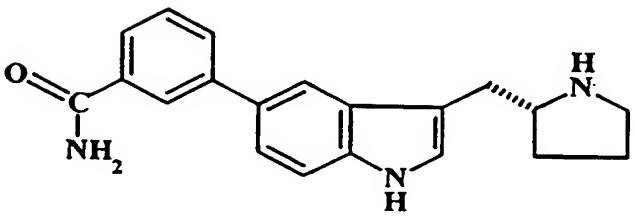
5-(3-Carbamoylphenyl)-3-(pyrrolidin-2(R)-ylmethyl)-1H-indole



(Preparation 40)

10% Pd/C, 1 bar H_2

CH_3COCl, CH_3CH_2OH



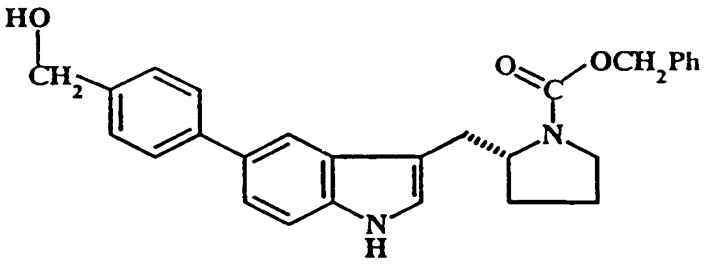
(title compound)

^{1}H-N.M.R. ($CDCl_3$/D_6-DMSO): δ = 1.40-1.55(m,1H), 1.70-2.00(m,3H), 2.80-2.90(m,1H), 2.90-3.10(m,3H), 3.40-3.50(m,1H), 4.72(s,2H), 5.25(s,3/4H), 7.15(s,1H), 7.35(d,1H), 7.35-7.45(m,2H), 7.55(d,1H), 7.70(s,1H), 7.80(s,1H), 8.70(s,1H).

EXAMPLE 37

This Example illustrates the preparation of:

5-(4-Hydroxymethylphenyl)-3-(pyrrolidin-2(R)-ylmethyl)-1H-indole



(Preparation 39)

10% Pd/C, 1 bar H_2

CH_3CH_2OH

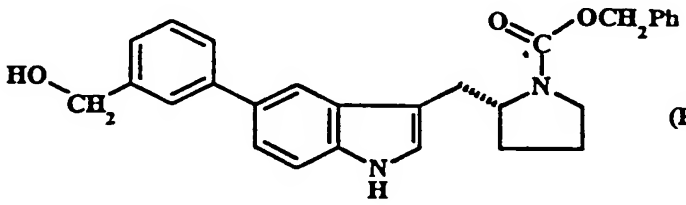
(title compound)

3-(1-Benzyloxycarbonylpyrrolidin-2(R)-ylmethyl)-5-(4-hydroxymethylphenyl)-1H-indole (450mg, 0.973mmol) (see Preparation 39) in ethanol was reduced using catalytic hydrogenation as described in Example 35 except that no acetyl chloride was used in the reaction. This gave the title compound as an off-white powder, m.pt. 65-69°C (210mg). Found: C,76.15; H,7.43; N,8.66; $C_{20}H_{22}N_2O.\frac{1}{2}H_2O$ requires: C,76.16; H,7.35; N,8.88%.

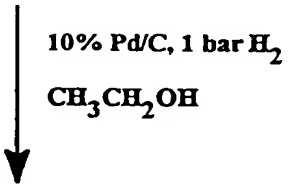
EXAMPLE 36

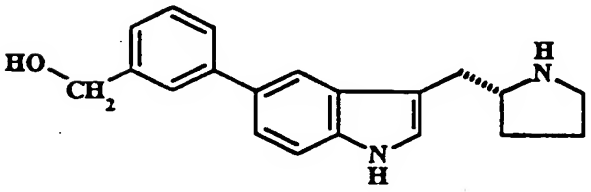
This Example illustrates the preparation of:

5-(3-Hydroxymethylphenyl)-3-(pyrrolidin-2(R)-ylmethyl)-1H-indole



(Preparation 38)





(title compound)

3-(1-Benzyloxycarbonylpyrrolidin-2(R)-ylmethyl)-5-(3-hydroxymethylphenyl)-1H-indole (1.030g, 2.316mmol) (see Preparation 38) in ethanol was reduced using catalytic hydrogenation as described in Example 35 except that no acetyl chloride was used in the reaction. This gave the title compound as an off-white foam (453mg).

Found: C,72.36; H,6.76; N,8.20; $C_{20}H_{22}N_2O.3/8CH_2Cl_2$ requires: C,72.35; H,6.78; N,8.28%.

$[\alpha]_D^{25}$ -21° (c=0.1 in methanol).

3-(1-Benzyloxycarbonylpyrrolidin-2(R)-ylmethyl)-5-(3-N,N-dimethylcarbamoylphenyl)-1H-indole (904mg, 1.80mmol) (see Preparation 37) was dissolved in ethanol (100ml) and acetyl chloride (130μL, 1.83mmol) was added dropwise to the resultant solution. 10% Palladium on carbon (300mg) was then added and the reaction stirred for 18 hours at room temperature under a pressure of 1 bar of hydrogen. The reaction was then halted and the catalyst removed by filtration through arbacel. Solvent removal under reduced pressure gave a white foam which was taken up in dichloromethane (250ml); washed with aqueous sodium carbonate and dried (Na_2SO_4). Solvent evaporation gave the crude product which was purified by column chromatography on silica gel, eluting with dichloromethane/ methanol/ammonium hydroxide (90:10:1) to afford, after combination and evaporation of the appropriate fractions, the title compound as a white foam, (583mg). Found: C,71.77; H,7.21; N,10.89; $C_{22}H_{25}N_3O.3/10\ CH_2Cl_2$ requires: C,71.82; H,6.92; N,11.27%.

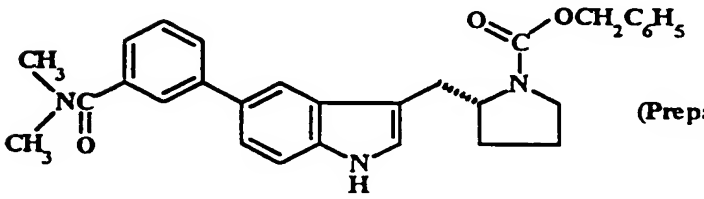
$[\alpha]_D^{25}$ -17° (c=0.1 in methanol).

^{1}H-N.M.R. ($CDCl_3$): δ = 1.40-1.55(m,1H), 1.65-2.00(m,3H), 2.70-3.30(m,10H), 3.35-3.50(m,1H), 5.30(s,3/5H), 7.05(s,1H), 7.30(d,1H), 7.30-7.50(m,3H), 7.60-7.75(m,2H), 7.80(s,1H), 8.60(s,1H).

EXAMPLE 35

This Example illustrates the preparation of:

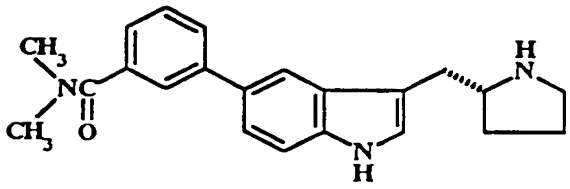
5-(3-N,N-Dimethylcarbamoylphenyl)-3-(pyrrolidin-2(R)-ylmethyl)-1H-indole



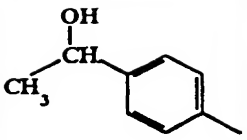
(Preparation 37)

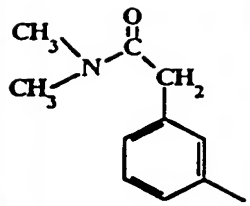
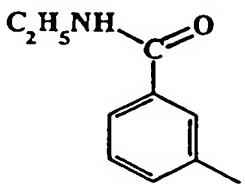
10% Pd/C, 15 PSI H_2

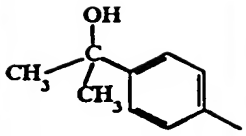
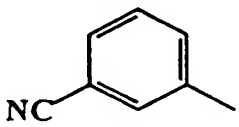
CH_3COCl, CH_3CH_2OH

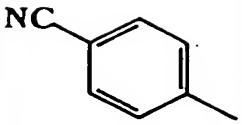
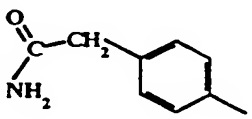


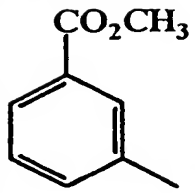
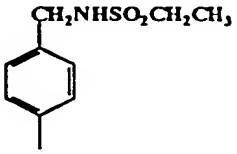
(title compound)

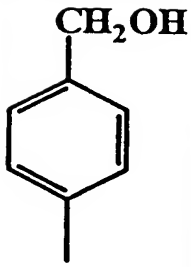
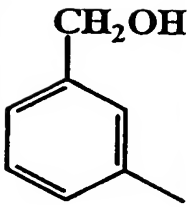
Ex No	R	Analysis (%)	^{1}H-NMR (in $CDCl_3$ unless otherwise stated)	$[\alpha]_D^{25}$ (c=0.1 in methanol)
34		Found: C,77.02; H,8.12; N,8.17; $C_{22}H_{26}N_2O.\frac{1}{2}H_2O$ requires C,76.93; H,7.92; N,8.17.	δ = 1.45-2.00 (m,4H); 1.60(d,3H), 2.15-2.30(m,1H), 2.35-2.55(m,1H), 2.50(s,3H), 2.55-2.70(m,1H), 3.10-3.30(m,2H), 4.90-5.00(q,1H), 7.05 (s,1H), 7.35-7.50 (m,4H), 7.65(d,2H), 7.80(s,1H), 8.10 (s,1H).	-

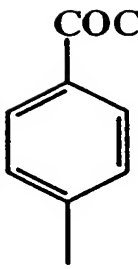
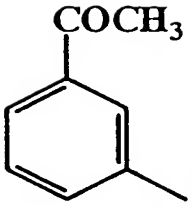
Ex No	R	Analysis (%)	^{1}H-NMR (in $CDCl_3$ unless otherwise stated)	$[\alpha]_D^{25}$ (c=0.1 in methanol)
32		Found: C,76.54; H,7.82; N,10.78; $C_{24}H_{29}N_3O$ requires C,76.77; H,7.78; N,11.18.	δ = 1.50-1.90 (m,4H), 2.15-2.30 (m,1H), 2.40-2.55 (m,1H), 2.50(s,3H), 2.55-2.90(m,1H), 3.00(s,3H), 3.05 (s,3H), 3.05-3.30 (m,2H), 3.80(s,2H), 7.05(s,1H), 7.20 (d,1H), 7.35-7.45 (m,3H), 7.50-7.55 (m,2H), 7.80(s,1H), 8.15(s,1H).	+65°
33		Found: C,75.44; H,7.58; N,11.22; $C_{23}H_{27}N_3O.1/3H_2O$ requires C,75.17; H,7.59; N,11.43.	δ = 1.25(t,3H), 1.45-1.90(m,4 2/3H), 2.15-2.30(m,1H), 2.40-2.55(m,1H), 2.50(s,3H), 2.55-2.70(m,1H), 3.10-3.30(m,2H), 3.55 (q,2H), 6.20(s,1H), 7.05(s,1H), 7.35-7.55(m,3H), 7.70 (d,1H), 7.75(d,1H), 7.80(s,1H), 8.00 (s,1H), 8.15(s,1H).	+74°

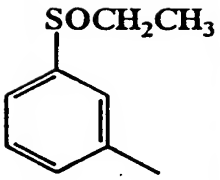
Ex No	R	Analysis (%)	^{1}H-NMR (in $CDCl_3$ unless otherwise stated)	$[\alpha]_D^{25}$ (c=0.1 in methanol)
30		Found: C,76.29; H,8.05; N,8.12; $C_{23}H_{28}N_2O.7/10$ H_2O requires C,76.50; H,8.21; N,7.76.	δ = 1.50-1.90 (m,5.4H), 1.60 (s,6H), 2.15-2.30 (m,1H), 2.40-2.55 (m,1H), 2.50(s,3H), 2.55-2.70(m,2H), 3.10-3.30(m,2H), 7.05(s,1H), 7.30-7.50(m,2H), 7.55 (d,2H), 7.65(d,2H), 7.80(s,1H), 8.10 (s,1H).	+72°
31		Found: C,73.06; H,6.52; N,12.24; $C_{21}H_{21}N_3.5/12CH_2$ Cl_2 requires C,73.33; H,6.27; N,11.98.	δ = 1.65-2.00 (m,4H), 2.40-2.65 (m,2H), 2.60(s,3H), 2.75-2.95(m,2H), 3.25-3.55(m,2H), 5.35(s,5/6H), 7.25 (s,1H), 7.35-7.65 (m,4H), 7.80(s,1H), 7.95(d,1H), 8.00 (s,1H), 8.55(s,1H).	+55°

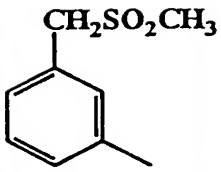
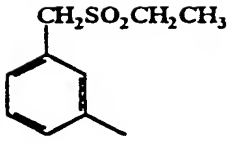
Ex No	R	Analysis (%)	^{1}H-NMR (in $CDCl_3$ unless otherwise stated)	$[\alpha]_D^{25}$ (c=0.1 in methanol)
28		Found: C,78.81; H,6.52; N,13.16; $C_{21}H_{21}N_3.¼H_2O$ requires C,78.84; H,6.77; N,13.13.	δ = 1.50-1.95(m,4H), 2.00-2.30(m,1.5H), 2.40-2.60(m,1H), 1.50 (s,1H), 2.60-2.75 (m,1H), 3.10-3.25 (m,2H), 7.10(s,1H), 7.25(s,1H), 7.40-7.50(m,2H), 7.65-7.85(m,4H), 7.80 (s,1H), 8.30(s,1H).	+90°
29		-	δ = 1.50-1.90 (m,4H), 2.15-2.30 (m,1H), 2.45(s,3H), 2.55-2.70(m,1H), 3.10-3.40(2H), 3.65(s,2H), 5.45 (s,2H), 7.05(s,1H), 7.25(d,2H), 7.35-7.45(m,2H), 7.65 (d,2H), 8.80(s,1H), 8.10(s,1H).	+62°

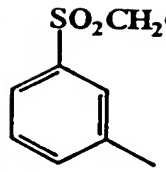
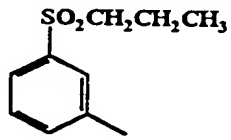
Ex No	R	Analysis (%)	^{1}H-NMR (in $CDCl_3$ unless otherwise stated)	$[\alpha]_D^{25}$ (c=0.1 in methanol)
26		-	($CDCl_3$/D_6-DMSO): δ = 1.30-1.48 (m,2H), 1.48-1.70(m,2H), 1.94-2.10(m,1H), 2.15-2.35(m, integral obscured by solvent), 2.25(s,3H), 2.38-2.50(m,1H), 2.82-3.05(m,2H), 3.70 (s,3H), 6.85(s,1H), 7.10-7.32(m, integral obscured by solvent), 7.54 (s,1H), 7.60(d,1H), 7.70(d,1H), 8.05 (s,1H), 9.80(s,1H) ppm.	+74°
27		Found: C,66.09; H,7.35; N,9.54; $C_{23}H_{29}N_3O_2S$.½H_2O requires: C,65.69; H,7.19; N,9.51.	δ = 1.37(t,3H), 1.45-1.90(m,5H), 2.18-2.30(m,1H), 2.37-2.57(m,1H), 2.47 (s,3H), 2.60-2.72 (m,1H), 3.00(q,2H), 3.08-3.30(m,2H), 4.35(s,2H), 4.60 (s,1H), 7.07(s,1H), 7.35-7.50(m,4H), 7.67(d,2H), 7.78 (s,1H), 8.17(s,1H) ppm.	+70°

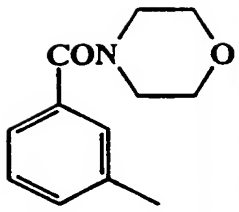
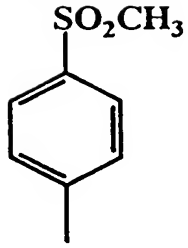
Ex No	R	Analysis (%)	^{1}-NMR (in $CDCl_3$ unless otherwise stated)	$[\alpha]_D^{25}$ (c=0.1 in methanol)
24		Found: C,75.38; H,7.55; N,8.44; $C_{21}H_{24}N_2O.3/4H_2O$ requires: C,75.53; H,7.70; N,8.39.	δ = 1.55-2.05 (m,6½H), 2.15-2.30(m,1H), 2.40-2.55(m,1H), 2.45(s,3H), 2.60-2.75(m,1H), 3.10-3.35(m,2H), 4.77 (s,2H), 7.05(s,1H), 7.40-7.45(m,2H), 7.45(d,2H), 7.67 (d,2H), 7.80(s,1H), 8.15(s,1H) ppm.	+59°
25		Found: C,74.35; H,7.86; N,8.51; $C_{21}H_{24}N_2O.H_2O$ requires: C,74.52; H,7.74; N,8.28.	δ = 1.50-1.72 (m,2H), 1.73-1.90(m,2H), 2.00-2.15(m,3H), 2.17-2.30(m,1H), 2.40-2.60(m,1H), 2.45(s,3H), 3.10-3.40(m,2H), 4.79 (s,2H), 7.05(s,1H), 7.35(d,1H), 7.40-7.50(m,3H), 7.61 (d,1H), 7.70(s,1H), 7.82(s,1H), 8.20 (s,1H) ppm.	+71°

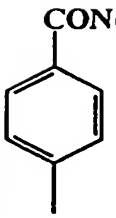
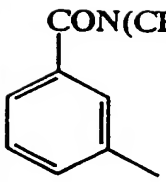
Ex No	R	Analysis (%)	^{1}H-NMR (in $CDCl_3$ unless otherwise stated)	$[\alpha]_D^{25}$ (c=0.1 in methanol)
22		Found: C,72.41; H,7.20; N,8.01; $C_{22}H_{24}N_2O.9/20CH_2Cl_2$ requires: C,72.75; H,7.55; N,7.56.	δ = 1.65-1.80 (m,2H); 1.80-2.06(m,2H), 2.35-2.60(m,1H), 2.52(s,3H), 2.65 (s,3H), 2.70-2.95 (m,2H), 3.15-3.47 (m,2H), 5.30(s, 9/10 H), 7.20 (s,1H), 7.40-7.52 (m,2H), 7.72(d,2H), 7.80(s,1H), 8.05 (d,2H), 8.37(s,1H) ppm.	+53°
23		Found: C,76.35; H,7.03; N,8.25; $C_{22}H_{24}N_2O.1/5CH_2Cl_2$ requires: C,76.31; H,7.04; N,8.02.	δ = 1.50-1.91 (m,4H), 2.15-2.28(m,1H), 2.38-2.75(m,2H), 2.48(s,3H), 2.68 (s,3H), 3.10-3.30 (m,2H), 7.10(s,1H), 7.40-7.50(m,2H), 7.55(dd,1H), 7.80 (s,1H), 7.87(d,1H), 7.92(d,1H), 8.15 (s,1H), 8.25(s,1H) ppm.	+58°

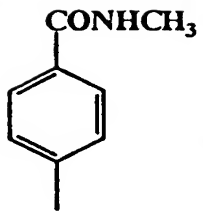
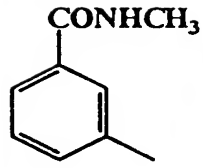
Ex No	R	Analysis (%)	^{1}H-NMR (in $CDCl_3$ unless otherwise stated)	$[\alpha]_D^{25}$ (c=0.1 in methanol)
20		Found: C,68.66; H,7.06; N,7.52; $C_{21}H_{24}N_2OS.4/5H_2O$ requires: C,68.74; H,7.03; N,7.63.	δ = 1.40-1.90 (m,5.6H), 2.17-2.30(m,1H), 2.40-2.55(m,1H), 2.45 (s,3H), 2.65-2.75 (m,1H), 2.79(s,3H), 3.05-3.30(m,2H), 7.07(s,1H), 7.45-7.50(m,2H), 7.55-7.65(m,2H), 7.75-7.80(m,1H), 7.80 (s,1H), 7.92(s,1H), 8.20(s,1H) ppm.	-
21		Found: C,69.04; H,7.37; N,7.27; $C_{22}H_{26}N_2OS.9/10H_2O$ requires: C,69.04; H,7.32; N,7.31.	δ = 1.25(t,3H), 1.50-1.95(m,5.8H), 2.16-2.30(m,1H), 2.38-2.58(m,1H), 2.48(s,3H), 2.60-2.72(m,1H), 2.78-3.05(m,2H), 3.08-3.30(m,2H), 7.10 (s,1H), 7.38-7.50 (m,2H), 7.50-8.05 (m,2H), 7.78(d,1H), 7.80(s,1H), 7.88 (s,1H), 8.25(s,1H) ppm.	-

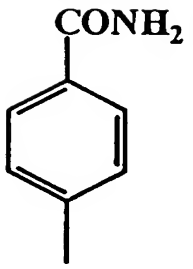
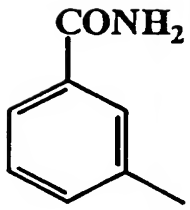
Ex No	R	Analysis (%)	^{1}H-NMR (in $CDCl_3$ unless otherwise stated)	$[\alpha]_D^{25}$ (c=0.1 in methanol)
18		-	δ = 1.45-1.90 (m,4H); 2.15-2.30(m,1H), 2.37-2.57(m,1H), 2.43(s,3H), 2.60-2.72(m,1H), 2.80 (s,3H), 3.10-3.30 (m,2H), 4.35(s,2H), 7.07(s,1H), 7.38 (d,1H), 7.39-7.42 (m,2H), 7.45 (dd,1H), 7.67 (s,1H), 7.70(d,1H), 7.75(s,1H), 8.12 (s,1H) ppm.	+81°
19		Found: C,67.72; H,7.16; N,7.11; $C_{23}H_{28}N_2O_2S$ .3/5H_2O requires: C,67.82; H,7.22; N,6.88.	δ = 1.42(t,3H), 1.55-1.95(m,5.2H), 2.15-2.42(m,1H), 2.45-2.60(m,1H), 2.50(s,3H), 2.62-2.78(m,1H), 2.95 (q,2H), 3.12-3.32 (m,2H), 4.35(s,2H), 7.10(s,1H), 7.40 (d,1H), 7.45-7.52 (m,2H), 7.55 (dd,1H), 7.65-7.75 (m,2H), 7.80(s,1H), 8.10(s,1H) ppm.	+45°

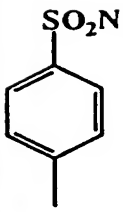
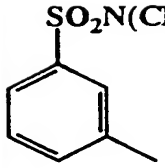
Ex No	R	Analysis (%)	^{1}H-NMR (in $CDCl_3$ unless otherwise stated)	$[\alpha]_D^{25}$ (c=0.1 in methanol)
16		Found: C,68.89; H,7.09; N,7.62; $C_{22}H_{26}N_2O_2S$ requires: C,69.08; H,6.85; N,7.32.	δ = 1.32(t,3H), 1.48-1.90(m,4H), 2.18-2.30(m,1H), 2.88-2.58(m,1H), 2.46 (s,3H), 2.60-2.72 (m,1H), 3.05-3.30 (m,4H), 7.10(s,1H), 7.38-7.50(m,2H), 7.62(dd,1H), 7.80 (s,1H), 7.82(d,1H), 7.92(d,1H), 8.12 (s,1H), 8.16(s,1H) ppm.	+79°
17		Found: C,69.27; H,7.29; N,7.29; $C_{23}H_{28}N_2O_2S$ requires: C,69.66; H,7.12; N,7.06.	δ = 1.02(t,3H), 1.50-2.00(m,6H), 2.20-2.37(m,1H), 2.40-2.65(m,1H), 2.47 (s,3H), 2.65-2.80 (m,1H), 3.05-3.17 (m,4H), 7.15(s,1H), 7.40-7.50(m,2H), 7.60(dd,1H), 7.80 (s,1H), 7.85(d,1H), 7.95(d,1H), 8.18 (s,1H), 8.25(s,1H) ppm.	+88°

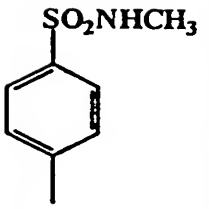
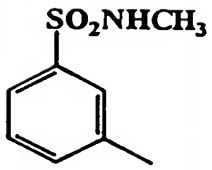
Ex No	R	Analysis (%)	^{1}H-NMR (in $CDCl_3$ unless otherwise stated)	$[\alpha]_D^{25}$ (c=0.1 in methanol)
14		Found: C,71.70; H,7.20; N,9.99; $C_{25}H_{29}N_3O_2.1/5CH_2Cl_2$ requires: C,71.41; H,6.95; N,9.99.	δ = 1.50-1.70 (m,2H); 1.70-1.90(m,2H), 2.15-2.28(m,1H), 2.30-2.55(m,1H), 2.45(s,3H), 2.60-2.70(m,1H), 3.08-3.30(m,2H), 3.40-3.95(m,8H), 5.30 (s,2/5H), 7.05 (s,1H), 7.36(d,1H), 7.38-7.42(m,2H), 7.48(dd,1H), 7.70 (s,1H), 7.72(d,1H), 7.78(s,1H), 8.28 (s,1H) ppm.	-84°
15		-	δ = 1.50-1.88 (m,4H), 2.17-2.30(m,1H), 2.40-2.55(m,1H), 2.47(s,3H), 2.62-2.72(m,1H), 3.05-3.30(m,2H), 3.12 (s,3H), 7.10(s,1H), 7.40-7.50(m,2H), 7.63(dd,1H), 7.80 (s,1H), 7.90(d,1H), 7.92(d,1H), 8.18 (s,1H), 8.21(s,1H) ppm.	+102°

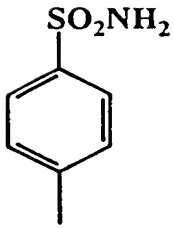
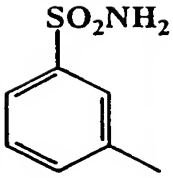
Ex No	R	Analysis (%)	^{1}H-NMR (in $CDCl_3$ unless otherwise stated)	$[\alpha]_D^{25}$ (c=0.1 in methanol)
12		Found: C,73.45; H,7.44; N,11.03; $C_{23}H_{27}N_3O.3/4H_2O$ requires: C,73.67; H,7.66; N,11.21.	δ = 1.50-1.70 (m,2H), 1.70-1.92(m,3½H), 2.15-2:30(m,1H), 2.40-2.55(m,1H), 2.48(s,3H), 2.58-2.70(m,1H), 2.95-3.30(m,8H), 7.07 (s,1H), 7.38-7.45 (m,2H), 7.50(d,2H), 7.68(d,2H), 7.80 (s,1H), 8.26(s,1H) ppm.	+60°
13		Found: C,72.92; H,7.45; N,10.80; $C_{23}H_{27}N_3O.¼CH_2Cl_2$ requires: C,72.97; H,7.24; N,10.98.	δ = 1.50-1.70 (m,2H), 1.70-1.90(m,2H), 2.15-2.30(m,1H), 2.35-2.57(m,1H), 2.45(s,3H), 2.57-2.70(m,1H), 2.90-3.30(m,2H), 3.05 (s,3H), 3.18(s,3H), 5.30(s,½H), 7.07 (s,1H), 7.35(d,1H), 7.38-7.42(m,2H), 7.45(dd,1H), 7.65-7.75(m,2H), 7.80 (s,1H), 8.28(s,1H) ppm.	+38°

Ex No	R	Analysis (%)	^{1}H-NMR (in $CDCl_3$ unless otherwise stated)	$[\alpha]_D^{25}$ (c=0.1 in methanol)
10		Found: C,73.12; H,7.33; N,11.27; $C_{22}H_{25}N_3O.3/4H_2O$ requires: C,73.20; H,7.40; N,11.64.	δ = 1.25(s,1½H), 1.50-1.70(m,2H), 1.70-1.92(m,2H), 2.15-2.30(m,1H), 2.38-2.60(m,1H), 2.50 (s,3H), 2.60-2.75 (m,1H), 2.95-3.15 (m,5H), 6.25(s,1H), 7.10(s,1H), 7.35-7.50(m,2H), 7.70 (d,2H), 7.80(s,1H), 7.82(d,2H), 8.30 (s,1H) ppm.	+74°
11		Found: C,73.98; H,7.43; N,11.72; $C_{22}H_{25}N_3O.½H_2O$ requires: C,74.13; H,7.35; N,11.79.	(D_6-DMSO): δ = 1.38-1.78(m,4H), 1.95-2.15(m,1H), 2.20-2.40(m,1H), 2.35 (s,3H), 2.40-2.60 (m,1H), 2.70-3.12 (m,5H), 7.18(s,1H), 7.30-7.45(m,2H), 7.58(dd,1H), 7.70 (d,1H), 7.75-7.88 (m,2H), 8.10(s,1H), 8.52(s,1H) ppm.	+87°

Ex No	R	Analysis (%)	^{1}H-NMR (in $CDCl_3$ unless otherwise stated)	$[\alpha]_D^{25}$ (c=0.1 in methanol)
8		-	δ = 1.55-1.75 (m,2H), 1.75-1.90(m,2H), 2.18-2.30(m,1H), 2.40-2.60(m,1H), 2.51(s,3H), 2.60-2.75(m,1H), 3.10-3.30(m,2H), 6.13 (s,1H), 6.37(s,1H), 7.07(s,1H), 7.18-7.25(m,2H), 7.72 (d,2H), 7.82(s,1H), 7.90(d,2H), 8.75(s,1H) ppm.	+179°
9		-	δ = 1.55-1.75 (m,2H), 1.75-2.00(m,2H), 2.20-2.35(m,1H), 2.45-2.60(m,1H), 2.50(s,3H), 2.65-2.78(m,1H), 3.10-3.35(m,2H), 5.85 (s,1H), 6.28(s,1H), 7.10(s,1H), 7.45-7.55(m,2H), 7.58 (dd,1H), 7.78 (d,1H), 7.85(d,1H), 7.90(s,1H), 8.15 (s,1H), 8.35(s,1H) ppm.	+36°

Ex No	R	Analysis (%)	^{1}H-NMR (in $CDCl_3$ unless otherwise stated)	$[\alpha]_D^{25}$ (c=0.1 in methanol)
6		Found: C,62.04; H,6.74; N,9.57; $C_{22}H_{27}N_3O_2S$ .2/5 CH_2Cl_2 requires: C,62.35; H,6.49; N,9.74.	δ = 1.50-1.70 (m,2H), 1.70-1.90(m,2H), 2.15-2.30(m,1H), 2.40-2.60(m,1H), 2.48(s,3H), 2.60-2.80(m,1H), 2.77(s,6H), 3.10-3.30(m,2H), 5.30 (s,4/5H), 7.10 (s,1H), 7.44-7.52 (m,2H), 7.75-7.90 (m,5H), 8.20(s,1H) ppm.	+64°
7		Found: C,65.63; H,6.88; N,10.18; $C_{22}H_{27}N_3O_2S$.1/15 CH_2Cl_2 requires: C,65.69; H,6.77; N,10.40.	δ = 1.55-1.75 (m,2H), 1.75-1.95(m,2H), 2.20-2.35(m,1H), 2.40-2.85(m,2H), 2.50(s,3H), 2.77 (s,6H), 3.13-3.30 (m,2H), 7.12(s,1H), 7.40-7.50(m,2H), 7.60(dd,1H), 7.70 (d,1H), 7.79(s,1H), 7.88(d,1H), 8.05 (s,1H), 8.20(s,1H) ppm.	+54°

Ex No	R	Analysis (%)	^{1}H-NMR (in $CDCl_3$ unless otherwise stated)	$[\alpha]_D^{25}$ (c=0.1 in methanol)
4		Found: C,64.34; H,6.45; N,10.33; $C_{21}H_{25}N_3O_2S$ .3/20 CH_2Cl_2 requires: C,64.11; H,6.44; N,10.60.	δ = 1.50-1.70 (m,2H), 1.70-1.90(m,2H), 2.15-2.30(m,1H), 2.40-2.55(m,1H), 2.48(s,3H), 2.55-2.70(m,4H), 3.10-3.30(m,2H), 4.40 (s,1H), 7.10 (s,1H), 7.38-7.50 (m,2H), 7.79 (d,2H), 7.80 (s,1H), 7.90 (d,2H), 8.15 (s,1H) ppm.	+53°
5		Found: C,62.70; H,6.49; N,10.42; $C_{21}H_{25}N_3O_2S$.¼CH_2Cl_2 requires: C,63.00; H,6.35; N,10.38.	δ = 1.50-1.95 (m,4H), 2.15-2.30(m,1H), 2.40-2.60(m,1H), 2.47(s,3H), 2.50 (s,3H), 2.60-2.80(m,1H), 3.10-3.30 (m,2H), 4.47 (s,1H), 5.31 (s,½H), 7.10 (s,1H), 7.38-7.50 (m,2H), 7.58 (dd,1H), 7.75-7.92(m,3H), 8.15 (s,1H), 8.17 (s,1H) ppm.	+48°

Ex No	R	Analysis (%)	^{1}H-NMR (in $CDCl_3$ unless otherwise stated)	$[\alpha]_D^{25}$ (c=0.1 in methanol)
2		-	(D_6-DMSO/$CDCl_3$): δ = 1.10-1.55 (m,4H), 1.90-2.00(m,1H), 2.10-2.25(m,1H), 2.17(s,3H), 2.25-2.40(m,1H), 2.60-3.00(m, integral obscured by solvent), 6.78 (s,1H), 7.05 (d,1H), 7.13 (d,1H), 7.43 (d,2H), 7.45 (s,1H), 7.65 (d,2H), 9.98(s,1H) ppm.	-
3		-	(D_6-DMSO/$CDCl_3$): δ = 1.25-1.65 (m,4H), 1.90-2.10(m,1H), 2.15-2.50(m, integral obscured by solvent), 2.25(s,3H), 2.78-3.00(m,2H), 6.45 (s,1H), 6.85 (s,1H), 7.12-7.33(m, integral obscured by solvent), 7.55(s,1H), 7.57 (d,1H), 7.87 (s,1H), 9.83(s,1H) ppm.	-

acetonitrile (5 ml) was heated under reflux, under nitrogen, for 18 hours. The reaction mixture was then evaporated under reduced pressure and dichloromethane (25 ml) was added. The resultant solution was washed with aqueous sodium carbonate, dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography on silica gel, eluting with ethyl acetate/diethylamine (98:2) to afford, after combination and evaporation of the appropriate fractions, the title compound as a white foam, (189 mg). Found: C,68.17; H,6.81; N,7.53; $C_{21}H_{24}N_2O_2S.1/20$ CH_2Cl_2 requires: C,67.83; H,6.51; N,7.52%.

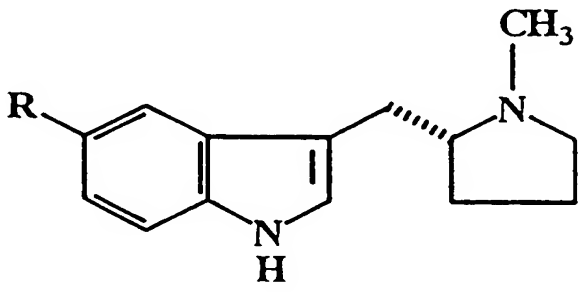
$[\alpha]_D^{25}$ + 63° (c=0.1 in methanol)

^{1}H-NMR ($CDCl_3$): δ = 1.50-1.70(m,2H), 1.70-1.90(m,2H), 2.15-2.30(m,1H), 2.40-2.57(m,1H), 2.50(s,3H), 2.60-2.77 (m,1H), 3.10-3.30(m,2H), 3.12(s,3H), 5.35(s,1/10 H), 7.10(s,1H), 7.45-7.50(m,2H), 7.82(d,2H), 7.85(s,1H), 8.00(d,2H), 8.22(s,1H) ppm.

EXAMPLES 2 TO 34

The compounds of the following tabulated Examples were prepared by similar methods to that of Example 1 using the appropriate phenyltri-n-butylstannane derivatives (see Preparations 2 to 12, 1, 13, 14 and 16 to 34) and 5-bromo-3-(1-methylpyrrolidin-2(R)-ylmethyl)-1H-indole as the starting materials.

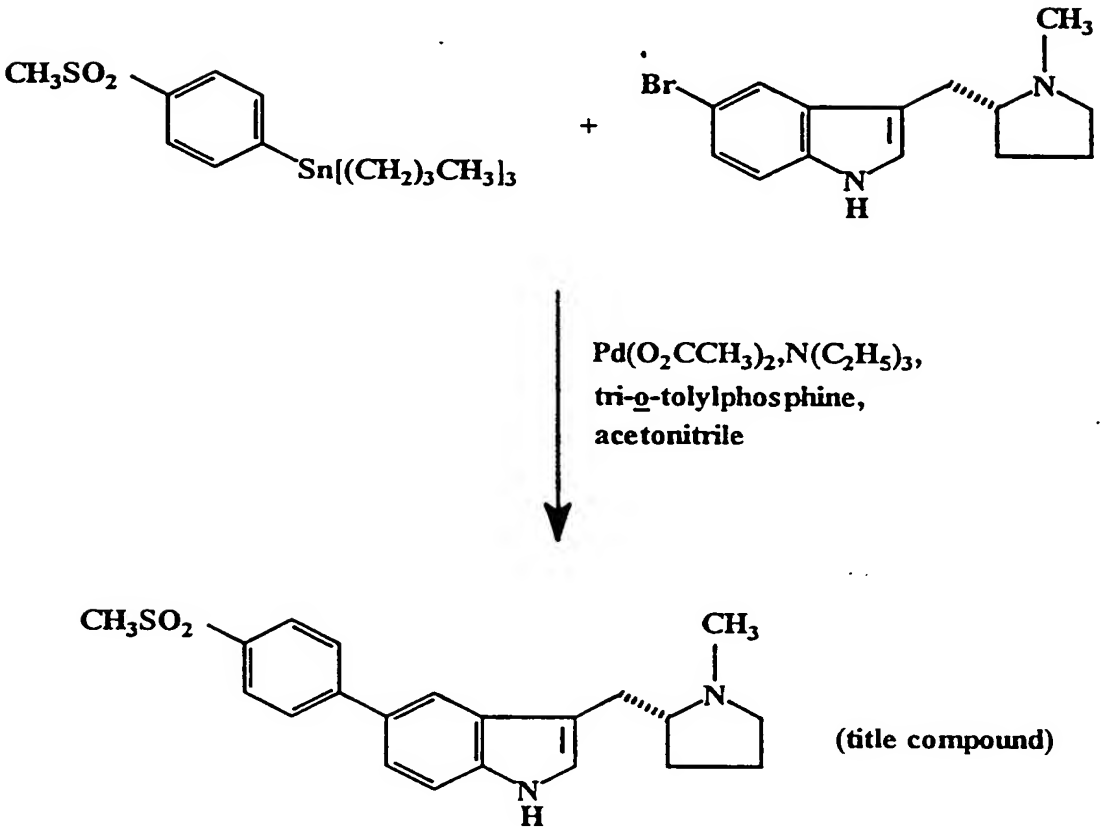
The compounds have the general formula:-



EXAMPLE 1

This Example illustrates the preparation of:

3-(1-Methylpyrrolidin-2(R)-ylmethyl)-5-(4-methylsulphonylphenyl)-1H-indole



(title compound)

A mixture of 4-methylsulphonylphenyltri-n-butylstannane (see Preparation 15) (680 mg, 1.53 mmol) tri-o-tolylphosphine (120 mg, 0.394 mmol), palladium(II) acetate (15 mg, 0.067 mmol), triethylamine (0.40 ml, 2.87 mmol) and 5-bromo-3-(1-methylpyrrolidin-2(R)-ylmethyl)-1H-indole (400 mg, 1.36 mmol) (see Preparation 36) in anhydrous

Examples 1 to 34, 47, 48 and 50 to 55 illustrate the cross-coupling process used to make the compounds of the present invention.

Examples 35 to 39 illustrate the preparation of N-pyrrolidines by the removal of a protecting group e.g. a benzyloxycarbonyl group from the N-atom of the pyrrolidine ring.

Examples 40 to 46 illustrate the alkylation of N-pyrrolidines e.g. those prepared in Examples 35, 38 and 39.

Examples 49, 63 and 66 illustrate the reduction of 5-substituted indole derivatives of the invention using lithium aluminium hydride.

Examples 56 and 57 illustrate the use of boron compounds (boranes) as coupling agents in place of the tin compounds (stannanes) of the preceding Examples.

Examples 58 and 59 illustrate the preparation of 5-substituted indoles of the invention by the removal of a protecting group (e.g. t-butoxycarbonyl) from the N-atom of the indole ring.

Examples 60 and 61 illustrate the process of Examples 1 to 34 to produce indole derivatives of the invention with a cyclopropylmethyl group on the N-atom of the pyrrolidine ring.

Examples 62, 64 and 65 illustrate the preparation of 5-substituted indole derivatives of the invention involving the removal from the N-atom of the indole ring of a silyl protecting group.

composition thereof, for the manufacture of a medicament for the curative or prophylatic treatment of migraine or an associated condition such as cluster headache, chronic paroxysmal hemicrania or headache associated with vascular disorders, or for the treatment of depression, anxiety, an eating disorder, obesity or drug abuse;

d) A method of treating a human being to cure or prevent migraine or an associated condition such as cluster headache, chronic paroxysmal hemicrania or headache associated with vascular disorders, or depression, anxiety, an eating disorder, obesity or drug abuse, which comprises treating said human being with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt or composition thereof;

e) The use of a compound of the formula (I), or of a pharmaceutically acceptable salt or composition thereof, for the manufacture of a medicament for the curative or prophylactic treatment of a medical condition for which a selective agonist of 5-HT_1-like receptors is indicated; and

f) A method of treating a human being to cure or prevent a medical condition for which a selective agonist of 5-HT_1-like receptors is indicated which comprises treating said human being with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt or composition thereof;

The following Examples illustrate the preparation of the compounds of the formula (I) and wherein:

The compounds of the formula (I) can also be administered intranasally or by inhalation and are conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer may contain a solution or suspension of the active compound. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the formula (I) and a suitable powder base such as lactose or starch.

Aerosol formulations are preferably arranged so that each metered dose or "puff" of aerosol contains 20 μg to 1000 μg of a compound of the formula (I) for delivery to the patient. The overall daily dose with an aerosol will be within the range 100 μg to 10 mg which may be administered in a single dose or, more usually, in divided doses throughout the day.

Thus the invention further provides:-

a) A pharmaceutical composition comprising a compound of the formula (I), or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier;

b) A compound of the formula (I), or a pharmaceutically acceptable salt or composition thereof, for use as a medicament;

c) The use of a compound of the formula (I), or of a pharmaceutically acceptable salt or

They can be injected parenterally, for example, intravenously, intramuscularly or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood.

For buccal or sublingual administration the compounds of the formula (I) may be administered in the form of tablets or lozenges which can be formulated in a conventional manner.

For oral, parenteral, buccal and sublingual administration to patients the daily dosage level of the compounds of the formula (I) and their salts will be from 0.01 to 20 mg/kg (in single or divided doses). Thus tablets or capsules of the compounds will contain from 5mg to 0.5g of active compound for administration singly or two or more at a time, as appropriate. The physician in any event will determine the actual dosage which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case; there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

Alternatively, the compounds of formula (I) can be administered in the form of a suppository or pessary, or they may be applied topically in the form of a lotion, solution, cream, ointment or dusting powder. For example, they can be incorporated into a cream consisting of an aqueous emulsion or polyethylene glycols or liquid paraffin; or they can be incorporated, at a concentration between 1 and 10%, into an ointment consisting of a white wax or white soft paraffin base together with such stabilizers and preservatives as may be required.

The compounds of the formula (I) and their salts are selective agonists at the "5-HT_1-like" subtype of 5-hydroxytryptamine receptor and are therefore useful in the curative or prophylactic treatment of migraine and associated conditions such as cluster headache, chronic paroxysmal hemicrania and headache associated with vascular disorders. Certain compounds of the formula (I) are also agonists at central 5-HT_1 receptors and are therefore useful for the treatment of depression, anxiety, eating disorders, obesity and drug abuse.

The in vitro evaluation of the "5-HT_1-like" receptor agonist activity of the compounds of the formula (I) is carried out by testing the extent to which they mimic sumatriptan in contracting the dog isolated saphenous vein strip (P.P.A. Humphrey et al., Br. J. Pharmacol., 94, 1123 (1988)). This effect can be blocked by methiothepin, a known 5-HT antagonist. Sumatriptan is known to be useful in the treatment of migraine and produces a selective increase in carotid vascular resistance in the anaesthetized dog and a consequent decrease in carotid arterial blood flow. It has been suggested (W. Feniuk et al., Br. J. Pharmacol., 96, 83 (1989)) that this is the basis of its efficacy.

In therapy, the compounds of the formula (I) and their salts can be administered alone, but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they can be administered orally in the form of tablets containing such excipients as starch or lactose, or in capsules or ovules either alone or in admixture with excipients, or in the form of elixirs, solutions or suspensions containing flavouring or colouring agents.

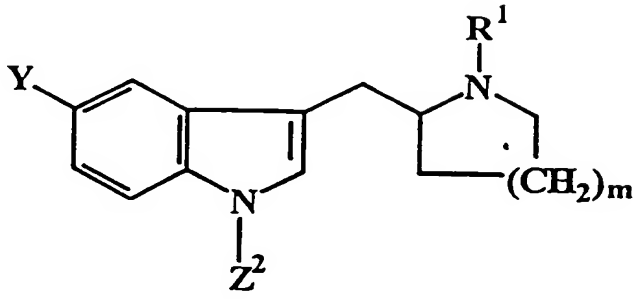
The reaction is preferably carried out at an elevated temperature and under an inert atmosphere, e.g. at the reflux temperature of the solvent and under nitrogen.

A compound of formula (XIV) may be obtained from a compound of formula (III) using standard methodology; for example, when Z^2 is trialkylsilyl (e.g. triisopropylsilyl or t-butyldimethylsilyl), by treating a compound of formula (III) with a suitable base, such as potassium hydride, in a suitable solvent, such as tetrahydrofuran and then reacting the resultant anion with a suitable silylating agent, such as the corresponding trialkylsilyl trifluoromethanesulphonate or the corresponding trialkylsilyl chloride; for example, when Z^2 is alkoxycarbonyl, e.g. t-butyloxycarbonyl, by treating with a suitable alkoxycarbonylating agent e.g. di-t-butyldicarbonate in a suitable solvent e.g. acetonitrile and, where appropriate, in the presence of a suitable catalyst e.g. 4-dimethylaminopyridine.

All of the above reactions are conventional and appropriate reagents and reaction conditions for their performance and procedures for isolating the desired products will be well known to those skilled in the art, in accordance with literature precedents and by reference to the Examples and Preparations hereto.

A pharmaceutically acceptable acid addition salt is readily prepared by mixing together solutions containing the free base and the desired acid. The salt generally precipitates from solution and is collected by filtration, or is recovered by evaporation of the solvent.

Compounds of formula (XIII) can be prepared by suitable metalation of a compound of formula:



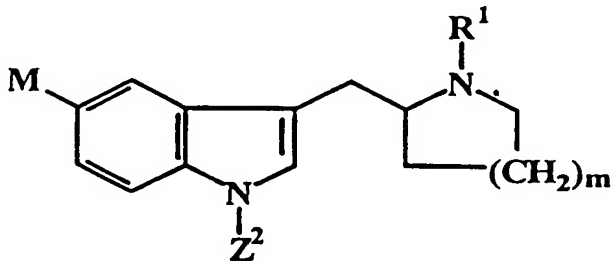
...(XIV)

wherein R^1, Z^2 and m are as defined above for a compound of formula (XIII) and Y is halo, preferably bromo, or $-OSO_2CF_3$.

In a typical procedure for the preparation of a compound of the formula (XIV) wherein M is a trialkylstannane, e.g. tri-n-butylstannane, a compound of the formula (XIV) is reacted with n-butyllithium (solution in hexanes) in a suitable solvent, e.g. tetrahydrofuran and the resultant solution is treated with the corresponding trialkylstannylhalide, e.g. tri-n-butylstannylchloride, or the corresponding hexaalkyldistannane e.g. hexa-n-butyldistannane.

In an alternative typical procedure for the preparation of a compound of formula (XIII) wherein M is trialkylstannane, e.g. tri-n-butylstannane a compound of the formula (XIV) is reacted with a hexaalkyldistannane e.g. hexa-n-butyldistannane, in the presence of a suitable catalyst, e.g. palladium (II) acetate, a suitable base; e.g. triethylamine, a suitable triarylphosphine, e.g. tri-o-tolylphosphine, and in a suitable solvent, e.g. acetonitrile.

wherein R is as defined for a compound of the formula (I) and X is halo or trifluoromethanesulphonyl, with a compound of the formula:-

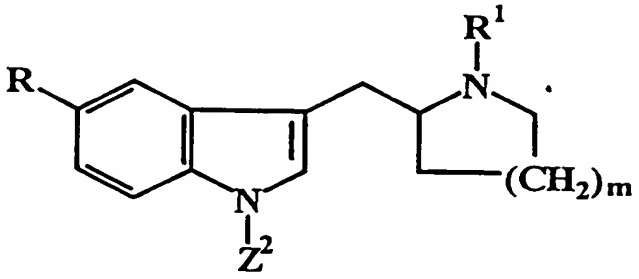


...(XIII)

wherein R^1 and m are as defined for a compound of the formula (XI), Z^2 is as defined above for formula (XI) and M is as defined in formula (II), e.g. a trialkylstannane such as tri-n-butylstannane; e.g. a dialkylborane such as diethylborane; lithium; halomagnesium; chlorozinc; copper; aryl or chloromercury; dihydroxyborane; dialkoxyborane. Such reactions should be carried out in the presence of a suitable palladium or nickel catalyst. The type of catalyst will vary with the character of M, the substrate and the structure of the compounds of formula (XIII) and (XII).

In a typical procedure a compound of formula (XIII) where M is tri-n-butylstannane, is reacted with a compound of formula (XII) in the presence of a suitable palladium catalyst, e.g. tetrakistriphenylphosphinepalladium (O), in a suitable solvent, e.g. toluene. The reaction can be carried out at from room temperature to, and preferably at, the reflux temperature of the solvent and is preferably carried out under an inert atmosphere, e.g. under nitrogen or argon.

5. Compounds of formula (I) can be prepared by suitable indole N-deprotection of a compound of formula:-



...(XI)

wherein R, R^1 and m are as defined for a compound of the formula (I) but R^1 is not hydrogen, or R^1 is a protecting group Z^1 wherein Z^1 is $-COOR^8$ wherein R^8 is as defined for formula (VIII) and Z^2 is a suitable indole N-protecting group such as: an alkoxycarbonyl group e.g. t-butyloxycarbonyl or a trialkylsilyl group e.g. triisopropylsilyl, e.g. t-butyldimethylsilyl. Suitable indole N-deprotection of a compound of formula (XI) can be achieved using standard methodology; for example, when Z^2 is t-butyloxycarbonyl, by protonolysis using trifluoroacetic acid or hydrogen chloride or, when Z^2 is trialkylsilyl, by protonolysis using hydrogen chloride or by treatment with an appropriate fluoride source such as tetra-n-butylammonium fluoride.

Compounds of formula (XI) can be prepared by suitably catalysed cross coupling of a compound of formula:

R-X (XII)

f) A compound of the formula (I) wherein R^2 is $NHSO_2R^7$ can be prepared from a compound of the formula (I) wherein R^2 is $NHCOR^7$ by first generating the corresponding primary amine as in method 5(e) above, followed by reaction thereof with the appropriate alkanesulphonyl halide (preferably the chloride) or alkanesulphonic anhydride, optionally in the presence of an additional base.

g) A compound of the formula (I) wherein R^2 is COR^7 can be prepared from a compound of the formula (I) wherein R^2 is CN by first reacting with a Grignard reagent of the formula:-

$$(C_1\text{-}C_6 \text{ alkyl})MgY^3$$

wherein Y^3 is chloro, bromo or iodo, followed by hydrolysis of the imine intermediate obtained.

h) A compound of formula (I) wherein R^2 is OH can be prepared from a compound of formula (I) wherein R^2 is COR^7 or wherein R^2 is CO_2R^7 by treatment with a suitable reducing agent e.g. lithium aluminium hydride or by treatment with a suitable metaloalkane reagent, e.g. a Grignard reagent of the formula $(C_1\text{-}C_4 \text{ alkyl})MgY^3$ wherein Y^3 is chloro, bromo or iodo.

b) A compound of the formula (I) wherein R^2 is $CONR^3R^4$ can also be prepared from a compound of the formula (I) wherein R^2 is CO_2R^7 by first hydrolysing the ester to the corresponding carboxylic acid using standard conditions, followed by either:

(i) condensation of the acid with an amine of the formula:-

HNR^3R^4

under standard peptide coupling conditions, e.g. using dicyclohexylcarbodiimide or N,N'-carbonyldiimidazole; or

(ii) conversion of the acid to a corresponding acyl halide, e.g. the chloride or bromide, followed by reaction with an amine of the formula:-

HNR^3R^4,

optionally in the presence of an additional base.

c) A compound of the formula (I) wherein R^2 is $CONH_2$ can be prepared from a compound of the formula (I) wherein R^2 is CN by a controlled hydrolysis, e.g. using concentrated sulphuric acid.

d) A compound of the formula (I) wherein R^2 is SO_2R^7 can be prepared from a compound of the formula (I) wherein R^2 is SOR^7 by oxidation with a suitable oxidising agent, e.g. meta-chloroperbenzoic acid or hydrogen peroxide.

e) A compound of the formula (I) wherein R^2 is $NHCONR^3R^4$ wherein R^3 and/or R^4 is C_1-C_6 alkyl or hydrogen can be prepared from a compound of the formula (I) wherein R^2 is $NHCOR^7$ by first hydrolysing the amide to the corresponding primary amine using standard conditions, followed by reaction of the amine with an isocyanate of the formula (C_1-C_6 alkyl)NCO.

In a typical procedure a compound of the formula (II) wherein M is a trialkylstannane moiety, e.g. tri-n-butylstannane, is reacted with a compound of the formula (VIII) in the presence of a suitable palladium catalyst, e.g. palladium (II) acetate, a suitable triarylphosphine, e.g. tri-o-tolylphosphine, a suitable base, e.g. triethylamine, and in a suitable solvent, e.g. acetonitrile. The reaction can be carried out at from room temperature to, and preferably at, the reflux temperature of the solvent and is preferably carried out under an inert atmosphere, e.g. under nitrogen or argon.

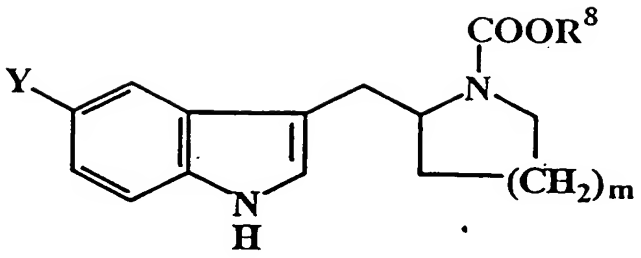
The intermediates of the formula (II) can be prepared as described previously.

4. Certain compounds of the formula (I) in which the substituent R^2 of the substituent group $-X-R^2$ on the phenyl or heterocyclic ring of R in formula (I) (and therefore forming part of R) is varied, can be prepared from other compounds of the formula (I) by functional group interconversion of the R^2 substituent as follows:-

a) A compound of the formula (I) wherein R^2 is $CONR^3R^4$ can be prepared from a compound of the formula (I) wherein R^2 is CO_2R^7 by reaction with an amine of the formula:-

$$HNR^3R^4.$$

The reaction is preferably carried out using an excess of the amine in a suitable solvent, e.g. a C_1-C_4 alkanol, and at an elevated temperature, e.g. at the reflux temperature of the solvent. For amines with a low boiling point the reaction is usually carried out in a sealed vessel.



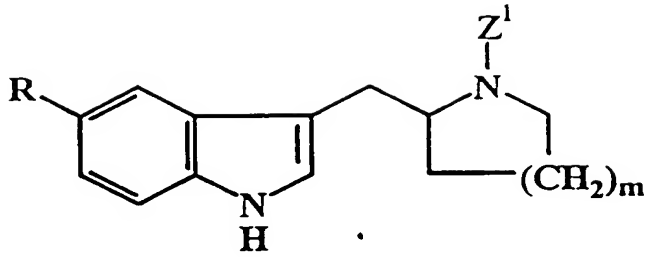
...(VIII)

wherein R^8, Y and m are as defined above.

Such a reaction should be carried out in the presence of a suitable catalyst such as a palladium or nickel catalyst. The type of catalyst used will vary with the character of M, the substrate and the structure of the compounds of formulae (II) and (VIII).

Suitable optionally substituted metal substituents for M above are described in Synthesis 1991, pages 413-432 (and the references described therein). Thus M can be, for example, any of the following:

$(alkyl)_3Sn$-, $(alkyl)_2B$-; $(HO)_2B$-; $(alkoxy)_2B$-, Li-; Cu-; chloroZn-; haloMg-; arylHg- or chloroHg-.



...(X)

wherein R is as defined above for formula (I) and Z^1 is a protecting group such as -$COOR^8$ where R^8 is as defined for compound (VIII).

This can be achieved using standard methodology, e.g. under acidic conditions when R^8 is t-butyl and by catalytic hydrogenation when R^8 is benzyl, to give a compound of the formula (IX).

Further useful non-hydrogenolytic N-deprotection procedures, when R^8 is benzyl, are either to employ hydrogen bromide in glacial acetic acid at about 0°C or a Lewis acid-catalysed nucleophilic deprotection using, for example, boron trifluoride etherate and excess ethanethiol in a suitable solvent such as dichloromethane at about room temperature.

Compounds of the formula (X) can be prepared by palladium-catalysed cross-coupling of a compound of the formula:-

RM (II)

wherein R is as defined above for a compound of formula (I) and M is an optionally substituted metal substituent suitable for cross-coupling reactions, with a compound of formula (VIII):

substituent. Depending on the nature of the ester, its deprotection may be achieved by acid or alkaline hydrolysis, protonolysis (e.g. when R^5 is t-butyl) or hydrogenolysis (e.g. when R^5 is benzyl). Conversion of the acid to the required amide may also be achieved by a variety of methods. For example, the acid may be activated by formation of the corresponding acyl halide, e.g. bromide or chloride, followed by reaction of the latter with an amine of formula R^3R^4NH optionally in the presence of a reaction-inert base to act as acid scavenger. Alternatively, any of a host of standard amide bond-forming (peptide coupling) reagents may be used. For example, the acid may be activated using a carbodiimide such as l-ethyl-3-dimethylamino-propylcarbodiimide, optionally in the presence of l-hydroxybenzotriazole and a reaction-inert amine such as N-methylmorpholine, followed by <u>in situ</u> reaction of the activated acid with an amine of formula R^3R^4NH;

(b) a compound of formula (III) wherein R^1 contains a R^5SO, or R^5SO_2 substituent is obtainable from the corresponding sulphide of formula (I), i.e. wherein R^1 contains a R^5S substituent, either by controlled oxidation using a stoichiometric amount of oxidising agent, or by using the required excess of oxidising agent, respectively. Suitable oxidising agents are, for example, a peracid such as meta-chloroperbenzoic acid, hydrogen peroxide or nitronium tetrafluoroborate.

Compounds of formula (IX) can be prepared by deprotection of a compound of formula (X):

(d) When R^1 is C_2-C_4 alkyl substituted at the 2-position with an electron withdrawing group such as R^5CO, R^6O_2C, R^3R^4NOC, $R^3R^4NO_2S$, R^5SO, R^5SO_2 and certain aryl and heteroaryl systems (e.g. 2- or 4-pyridyl), by conjugate addition (Michael-type reaction) of a compound of formula (IX) to the corresponding α,ß-unsaturated ketone-, ester-, amide-, sulphonamide-, sulphoxide-, sulphone-, arene- or heteroarene-containing R^1 precursor respectively, wherein R^3, R^4, R^5 and R^6 are as defined for formula (I), optionally in the presence of a tertiary amine base such as triethylamine. The reaction may optionally be conducted in a suitable solvent, e.g. N,N-dimethylacetamide, at from about 0°C to about 100°C, preferably at about 100°C.

3. Certain compounds of formula (I) can be prepared from other compounds of formula (I) by, for example, the following conventional functional group transformations within the R^1 substituent:-

(a) a compound of formula (I) wherein R^1 contains a R^3R^4NOC substituent is obtainable from a corresponding ester of formula (I), i.e. wherein R^1 contains a R^5O_2C substituent, by direct amination using an amine of formula R^3R^4NH. The reaction is preferably carried out using an excess of the amine in a suitable solvent such as a C_1-C_4 alkanol at an elevated temperature, e.g. the reflux temperature of the reaction medium. For low boiling amines, the reaction is preferably conducted in a sealed vessel.

The same over-all transformation can be effected indirectly <u>via</u> the intermediacy of the corresponding carboxylic acid, i.e. a compound of formula (III) wherein R^1 contains a HO_2C

In the case of a carboxylic acid precursor, the substrate (IX) and the said acid reagent may be reacted together in the presence of excess sodium borohydride in a suitable solvent; preferably the carboxylic acid itself is used as solvent whenever possible. Since this reductive alkylation proceeds via in situ formation of the corresponding sodium triacyloxy-borohydride, obvious variations are to employ preformed intermediate when commercially available or to preform it in a separate in situ step using the stoichiometric amount of carboxylic acid in a suitable solvent. An example of the latter procedure involves the treatment of six equivalents of the carboxylic acid with two equivalents of sodium borohyride in dry tetrahydrofuran at about room temperature. When formation of the required sodium triacyloxyborohydride is complete, the reaction mixture is treated with a solution of one equivalent of the substrate (IX) in the same solvent and the subsequent reaction step is conducted at from about room temperature to about 70°C, preferably 50-55°C.

(c) When R^1 is C_2-C_4 alkyl or C_3-C_7 cycloalkyl, each substituted at the 2-position with a hydroxy group, by reaction of a compound of formula (IX) with the appropriate epoxide-containing R^1 precursor, optionally in the presence of a tertiary amine base, e.g. triethylamine, and preferably in a suitable solvent such as C_1-C_4 alkanol. The reaction can be conducted at from about 0°C to about 150°C, preferably at from about room temperature to about 60°C.

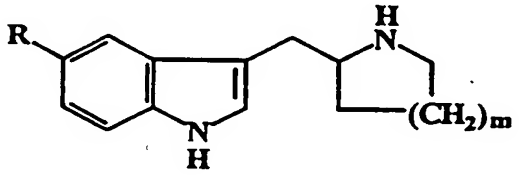
When R^1 is 2-hydroxyethyl, an "ethylene oxide equivalent" is preferably employed. Thus a compound of formula (IX) may be reacted with ethylene carbonate in a suitable solvent such as dimethylformamide at about 120°C.

(a) By reaction of a compound of formula (IX) with a compound of formula R^1X, wherein R^1 is as defined for formula (I), and X is a suitable leaving group, e.g. halo (preferably chloro, bromo or iodo), C_1-C_4 alkanesulphonyloxy, trifluoromethanesulphonyloxy or arylsulphonyloxy (preferably benzenesulphonyloxy or p-toluenesulphonyloxy), in the presence of an appropriate base, e.g. sodium or potassium carbonate or bicarbonate, or triethylamine, in a suitable solvent such as a C_1-C_4 alkanol, 1,2-dimethoxyethane, acetonitrile, dimethylformamide or N,N-dimethylacetamide, and optionally in the presence of sodium or potassium iodide. The reaction can be conducted at from about 0°C to about 150°C, preferably at from about room temperature to about 100°C.

(b) By reductive alkylation of a compound of formula (IX) using the appropriate aldehyde-, ketone- or carboxylic acid-containing R^1 precursor. In the case of an aldehyde or ketone precursor, the substrate (IX) and carbonyl reagent may be reacted together under conventional catalytic hydrogenation conditions or in the presence of sodium cyanoborohydride, in a suitable solvent such as methanol or ethanol, at about room temperature. Alternatively, the reductive alkylation may be achieved by a two-step procedure in which the intermediate enamine is formed initially under conventional conditions and subsequently reduced to the required amine, e.g. using sodium cyanoborohydride in tetrahydrofuran-methanol at about room temperature.

(b) a compound of formula (III) wherein R^1 contains a R^6SO, or R^6SO_2 substituent is obtainable from the corresponding sulphide of formula (I), i.e. wherein R^1 contains a R^6S substituent, either by controlled oxidation using a stoichiometric amount of oxidising agent, or by using the required excess of oxidising agent, respectively. Suitable oxidising agents are, for example, a peracid such as meta-chloroperbenzoic acid, hydrogen peroxide or nitronium tetrafluoroborate.

2. A compound of formula (I) may be obtained by selective N-alkylation of the saturated heterocyclic ring of a compound of formula (IX):



...(IX)

wherein R and m are as previously defined for formula (I), using one or more of the following methods.

Certain compounds of formula (III) can be prepared from other compounds of formula (III) by, for example, the following conventional functional group transformations within the R^1 substituent:-

(a) a compound of formula (I) wherein R^1 contains a R^3R^4NOC substituent is obtainable from a corresponding ester of formula (I), i.e. wherein R^1 contains a R^6O_2C substituent, by direct amination using an amine of formula R^3R^4NH. The reaction is preferably carried out using an excess of the amine in a suitable solvent such as a C_1-C_4 alkanol at an elevated temperature, e.g. the reflux temperature of the reaction medium. For low boiling amines, the reaction is preferably conducted in a sealed vessel.
The same over-all transformation can be effected indirectly via the intermediacy of the corresponding carboxylic acid, i.e. a compound of formula (III) wherein R^1 contains a HO_2C substituent. Depending on the nature of the ester, its deprotection may be achieved by acid or alkaline hydrolysis, protonolysis (e.g. when R^6 is t-butyl) or hydrogenolysis (e.g. when R^6 is benzyl). Conversion of the acid to the required amide may also be achieved by a variety of methods. For example, the acid may be activated by formation of the corresponding acyl halide, e.g. bromide or chloride, followed by reaction of the latter with an amine of formula R^3R^4NH optionally in the presence of a reaction-inert base to act as acid scavenger. Alternatively, any of a host of standard amide bond-forming (peptide coupling) reagents may be used. For example, the acid may be activated using a carbodiimide such as l-ethyl-3-dimethylamino-propylcarbodiimide, optionally in the presence of l-hydroxybenzotriazole and a reaction-inert amine such as N-methylmorpholine, followed by in situ reaction of the activated acid with an amine of formula R^3R^4NH;

substrate (IIIB) in the same solvent and the subsequent reaction step is conducted at from about room temperature to about 70°C, preferably 50-55°C.

(c) When R^1 is C_2-C_4 alkyl or C_3-C_7 cycloalkyl, each substituted at the 2-position with a hydroxy group, by reaction of a compound of formula (IIIB) with the appropriate epoxide-containing R^1 precursor, optionally in the presence of a tertiary amine base, e.g. triethylamine, and preferably in a suitable solvent such as C_1-C_4 alkanol. The reaction can be conducted at from about 0°C to about 150°C, preferably at from about room temperature to about 60°C.

When R^1 is 2-hydroxyethyl, an "ethylene oxide equivalent" is preferably employed. Thus a compound of formula (IIIB) may be reacted with ethylene carbonate in a suitable solvent such as dimethylformamide at about 120°C.

(d) When R^1 is C_2-C_4 alkyl substituted at the 2-position with an electron withdrawing group such as R^5CO, R^6O_2C, R^3R^4NOC, $R^3R^4NO_2S$, R^5SO, R^5SO_2 and certain aryl and heteroaryl systems (e.g. 2- or 4-pyridyl), by conjugate addition (Michael-type reaction) of a compound of formula (IIIB) to the corresponding α,ß-unsaturated ketone-, ester-, amide-, sulphonamide-, sulphoxide-, sulphone-, arene- or heteroarene-containing R^1 precursor respectively, wherein R^3, R^4, R^5 and R^6 are as defined for formula (I), optionally in the presence of a tertiary amine base such as triethylamine. The reaction may optionally be conducted in a suitable solvent, e.g. N,N-dimethylacetamide, at from about 0°C to about 100°C, preferably at about 100°C.

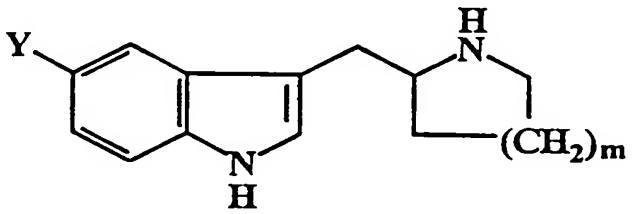
(b) By reductive alkylation of a compound of formula (IIIB) using the appropriate aldehyde-, ketone- or carboxylic acid-containing R^1 precursor. In the case of an aldehyde or ketone precursor, the substrate (IIIB) and carbonyl reagent may be reacted together under conventional catalytic hydrogenation conditions or in the presence of sodium cyanoborohydride, in a suitable solvent such as methanol or ethanol, at about room temperature. Alternatively, the reductive alkylation may be achieved by a two-step procedure in which the intermediate enamine is formed initially under conventional conditions and subsequently reduced to the required amine, e.g. using sodium cyanoborohydride in tetrahydrofuran-methanol at about room temperature.

In the case of a carboxylic acid precursor, the substrate (IIIB) and the said acid reagent may be reacted together in the presence of excess sodium borohydride in a suitable solvent; preferably the carboxylic acid itself is used as solvent whenever possible. Since this reductive alkylation proceeds via in situ formation of the corresponding sodium triacyloxy-borohydride, obvious variations are to employ preformed intermediate when commercially available or to preform it in a separate in situ step using the stoichiometric amount of carboxylic acid in a suitable solvent. An example of the latter procedure involves the treatment of six equivalents of the carboxylic acid with two equivalents of sodium borohyride in dry tetrahydrofuran at about room temperature. When formation of the required sodium triacyloxyborohydride is complete, the reaction mixture is treated with a solution of one equivalent of the

example, boron trifluoride etherate and excess ethanethiol in a suitable solvent such as dichloromethane at about room temperature.

Further processes for the preparation of the compounds of formula (III) and the intermediates used to prepare them are as follows:

1. A compound of formula (III) may be obtained by selective N-alkylation of the saturated heterocyclic ring of a compound of formula (IIIB):



...(IIIB)

wherein Y and m are as previously defined for formula (III), using one or more of the following methods.

(a) By reaction of a compound of formula (IIIB) with a compound of formula R^1X, wherein R^1 is as defined for formula (I), and X is a suitable leaving group, e.g. halo (preferably chloro, bromo or iodo), C_1-C_4 alkanesulphonyloxy, trifluoromethanesulphonyloxy or arylsulphonyloxy (preferably benzenesulphonyloxy or p-toluenesulphonyloxy), in the presence of an appropriate base, e.g. sodium or potassium carbonate or bicarbonate, or triethylamine, in a suitable solvent such as a C_1-C_4 alkanol, 1,2-dimethoxyethane, acetonitrile, dimethylformamide or N,N-dimethylacetamide, and optionally in the presence of sodium or potassium iodide. The reaction can be conducted at from about 0°C to about 150°C, preferably at from about room temperature to about 100°C.

wherein m and Y are as previously defined for a compound of the formula (III) and R^8 is benzyl or t-butyl.

In a typical procedure a 5-haloindole of the formula (V) is converted to a magnesium derivative by reaction with a suitable Grignard reagent, e.g. ethylmagnesium bromide or methylmagnesium iodide, in a suitable solvent, e.g. diethyl ether or tetrahydrofuran, and this derivative is then reacted in situ with an acid chloride of the formula (VI) to provide a 3-acylindole of the formula (VII).

The acid chlorides of the formula (VI) can be prepared by conventional methods such as from the corresponding carboxylic acids, e.g. using oxalyl chloride and a trace of N,N-dimethylformamide in dichloromethane.

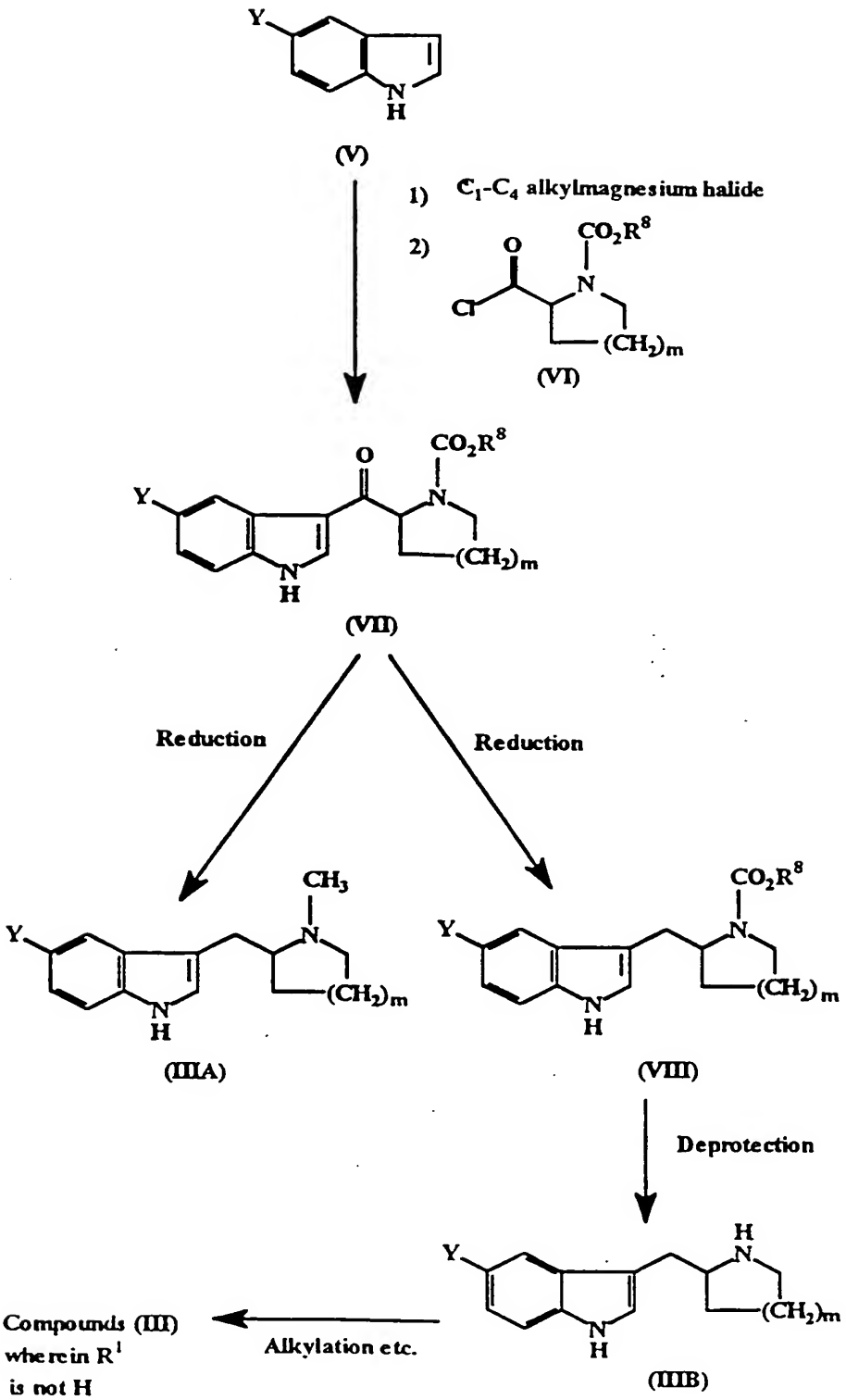
A compound of the formula (III) wherein R^1 is methyl (i.e. a compound of the formula (IIIA)) can be prepared directly from a compound of the formula (VII) by reduction with a suitable reducing agent, e.g. lithium aluminium hydride, in a suitable solvent, e.g. tetrahydrofuran.

A compound of the formula (VII) can be reduced to a compound of the formula (VIII) with a suitable reducing agent, e.g. lithium borohydride, in a suitable solvent, e.g. tetrahydrofuran.

Deprotection of a compound of the formula (VIII) can be achieved using standard methodology, e.g. under acidic conditions when R^8 is t-butyl and by catalytic hydrogenation when R^8 is benzyl, to give a compound of the formula (IIIB).

Further useful non-hydrogenolytic N-deprotection procedures, when R^8 is benzyl, are either to employ hydrogen bromide in glacial acetic acid at about 0°C or a Lewis acid-catalysed nucleophilic deprotection using, for

Scheme 1


Y
N
H
(V)
1) C_1-C_4 alkylmagnesium halide
2)
CO_2R^8
O
Cl
N
$(CH_2)_m$
(VI)
O
CO_2R^8
Y
N
H
$(CH_2)_m$
(VII)
Reduction
Reduction
CH_3
N
Y
H
$(CH_2)_m$
(IIIA)
CO_2R^8
N
Y
H
$(CH_2)_m$
(VIII)
Deprotection
H
N
Y
H
$(CH_2)_m$
(IIIB)
Alkylation etc.
Compounds (III)
wherein R^1
is not H

In a typical procedure a compound of the formula (II) wherein M is a trialkylstannane, e.g. tri-n-butylstannane, is reacted with a compound of the formula (III) in the presence of a suitable palladium catalyst, e.g. palladium (II) acetate, a suitable triarylphosphine, e.g. tri-o-tolylphosphine, a suitable base, e.g. triethylamine, and in a suitable solvent, e.g. acetonitrile. The reaction can be carried out at from room temperature to, and preferably at, the reflux temperature of the solvent and is preferably carried out under an inert atmosphere, e.g. under nitrogen or argon.

The intermediates of the formula (II) can be prepared by reacting a compound of the formula:-

$$R\text{-}Y^1 \qquad \ldots(IV)$$

wherein R is as defined for a compound of the formula (I) and Y^1 is halo, preferably bromo or iodo, or is $-OSO_2CF_3$, as appropriate.

Compounds of formula (II) can be prepared by suitable metalation of a compound of formula (IV).

For a typical procedure (when M is a trialkylstannane) a compound of formula (IV) is reacted with a hexaalkyldistannane, e.g. hexa-n-butyldistannane, in the presence of a suitable palladium catalyst, e.g. palladium (II) acetate, a suitable base, e.g. triethylamine, a suitable triarylphosphine, e.g. tri-o-tolylphosphine, and in a suitable solvent, e.g. acetonitrile. The reaction is preferably carried out at an elevated temperature and under an inert atmosphere, e.g. at the reflux temperature of the solvent and under nitrogen.

The intermediates of the formula (IV) can be prepared by conventional methods.

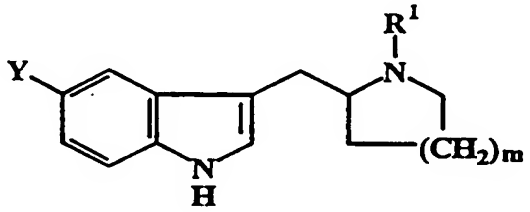
The intermediates of the formula (III) can be prepared as shown in Scheme 1:-

The compounds of the formula (I) which are provided by the present invention can be prepared by the following methods:-

1) All compounds of the formula (I) can be prepared by palladium-catalysed cross-coupling of a compound of the formula:-

RM (II)

wherein R is as defined above for a compound of formula (I) and M is an optionally substituted metal substituent suitable for cross-coupling reactions, with a compound of formula (III)



...(III)

wherein R^1 and m are as defined for a compound of the formula (I) and Y is iodo or bromo and is preferably bromo, or is $-OSO_2CF_3$. Such a reaction should be carried out in the presence of a suitable catalyst such as a palladium or nickel catalyst. The type of catalyst used will vary with the character of M, the substrate and the structure of the compounds of formulae (II) and (III).

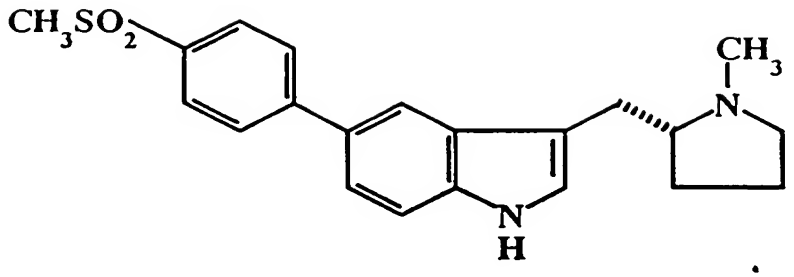
Suitable optionally substituted metal substituents for M above are described in Synthesis 1991, pages 413-432 (and the references described therein). Thus M can be, for example, any of the following:

$(alkyl)_3Sn$-, $(alkyl)_2B$-; $(HO)_2B$-; $(alkoxy)_2B$-, Li-; Cu-; chloroZn-; haloMg-; arylHg- or chloroHg-.

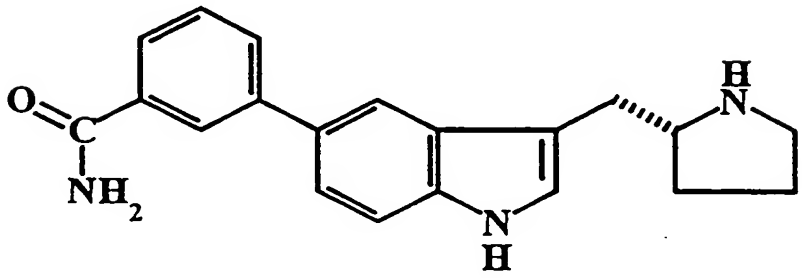
The pharmaceutically acceptable salts of the compounds of the formula (I) include acid addition salts formed with acids which form non-toxic salts such as the hydrochloride, hydrobromide, hydroiodide, sulphate, bisulphate, phosphate, hydrogen phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate, gluconate, benzoate, methanesulphonate, benzenesulphonate and para-toluenesulphonate salts. For a review on suitable pharmaceutical salts see Berge et al, J. Pharm. Sci., 66, 1-19 (1977).

The compounds of the formula (I) contain at least one chiral centre and therefore exist as at least one pair of enantiomers. The invention includes both the individual stereoisomers of the compounds of the formula (I) together with mixtures thereof. Separation of diastereoisomers may be achieved by conventional techniques, e.g. by fractional cystallisation, chromatography or H.P.L.C. of a diastereoisomeric mixture of a compound of the formula (I) or a suitable salt or derivative thereof. An individual enantiomer of a compound of the formula (I) may also be prepared from a corresponding optically pure intermediate or by resolution, either by H.P.L.C. of the racemate using a suitable chiral support or by fractional crystallisation of the diastereoisomeric salts formed by reaction of the racemate with a suitable optically active acid.

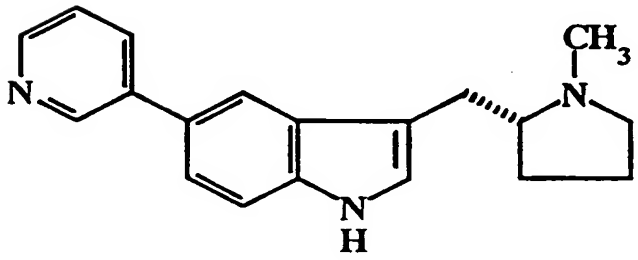
Certain compounds of the formula (I) can exist in different tautomeric forms. The invention includes the different tautomeric forms where appropriate.



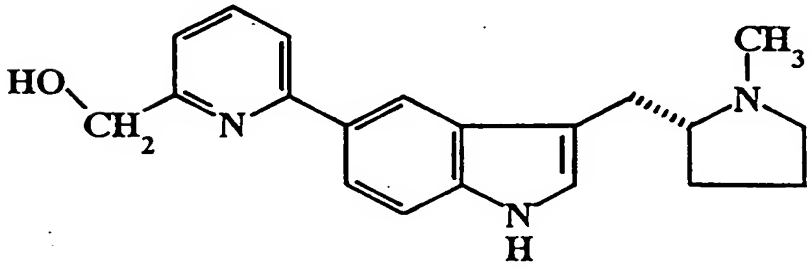
Compound of Example 1 ;



Compound of Example 38 ;



Compound of Example 56 ; and



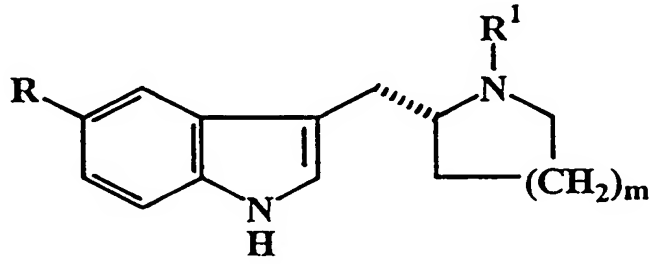
Compound of Example 63

X is a direct link or methylene; and

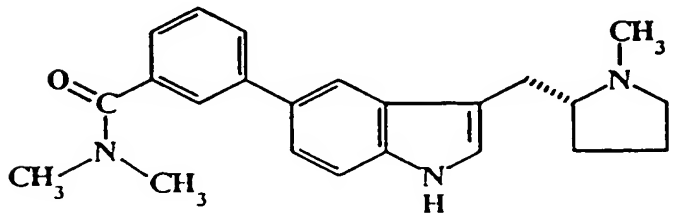
m is 1.

In an even more preferred aspect the invention provides compounds of formula I wherein R is phenyl optionally substituted at the 3- or 4-position, or 2-, 3- or 4-pyridinyl optionally substituted at the 5- or 6-position, both optionally substituted with sulphamoyl, N,N-dimethylsulphamoyl, carbamoyl, N-methylcarbamoyl, N,N-dimethylcarbamoyl, morpholinocarbonyl, methyl- or ethyl- or n-propyl-sulphonyl or -sulphinyl, methyl- or ethyl-sulphonylmethyl, acetyl, hydroxymethyl, methoxycarbonyl, ethanesulphonamidomethyl, cyano, carbamoylmethyl, 1-hydroxyprop-2-yl, N,N-dimethylcarbamoylmethyl, ethylcarbamoyl, dimethylcarbamoyl or methoxycarbonyl;
R^1 is hydrogen, methyl, ethyl, 2-methoxyethyl, cyclopropylmethyl, benzyloxycarbonyl, 2-carbamoylethyl, 2-dimethylcarbamoylethyl; and m is 1.

The preferred compounds of the formula (I) have the R-configuration at the 2-position of the pyrrolidine or piperidine ring, i.e.



Preferred compounds of the invention include the following:



Compound of Example 13 ;

Preferably R^3 and R^4 are either each independently selected from H and C_1-C_4 alkyl, or R^3 and R^4 taken together represent C_3-C_6 alkylene interrupted by O.

Most preferably R^3 and R^4 are either each independently selected from H, or C_1-C_4 alkyl, or R^3 and R^4 taken together with the nitrogen atom to which they are attached represent morpholino.

Preferably R^7 is methyl, ethyl or n-propyl.

Preferably X is a direct link or methylene.

Preferably m is 1.

In a further aspect, therefore, the invention provides compounds of formula (I) wherein:

R is substituted phenyl, pyridinyl, pyrimidinyl, thienyl or furyl, each optionally substituted by a group of the formula:

$$-X-R^2;$$

R^1 is H, C_1-C_6 alkyl, C_1-C_4 alkoxy(C_1-C_6)alkylene, $R^4R^3NCO(C_1$-$C_6)$alkylene, or C_3-C_6 cycloalkyl(C_1-C_4)alkylene;

R^2 is COR^7, CO_2R^7, SOR^7, SO_2R^7, $CONR^3R^4$, $SO_2NR^3R^4$, $NHSO_2R^7$, CN or OH;

R^3 and R^4 are either each independently selected from H and C_1-C_4 alkyl, or R^3 and R^4 taken together represent C_3-C_6 alkylene interrupted by O;

R^7 is methyl, ethyl or n-propyl;

n is 0, 1 or 2.

"aryl" for substituents other than R means phenyl optionally substituted by C_1-C_6 alkyl, C_1-C_6 alkoxy or halo; and

"heteroaryl" for substituents other than R means pyridinyl, pyrimidinyl, pyrazinyl, furyl, thienyl, pyrrolyl, thiazolyl or oxazolyl.

Alkyl, alkoxy and alkenyl groups having three or more carbon atoms, and alkynyl groups having four or more carbon atoms, can be straight- or branched-chain.

Halo means fluoro, chloro, bromo or iodo.

When R is phenyl, it is preferably substituted phenyl, the substituents being preferably at the 3- or 4-position of the ring.

A preferred groups of compounds of formula (I) is that wherein R^1 is $(R^5CO)C_1$-C_2 alkylene; $(R^6O_2C)C_1$-C_2 alkylene; $(R^3R^4NOC)C_1$-C_2 alkylene; $R^3R^4NO_2SCH_2CH_2$; R^3NSO_2 C_1-C_2 alkylene; R^3SOC_1-C_2 alkylene; $R^3SO_2C_1$-C_2 alkylene; $(R^5O)C_2$-C_3 alkylene; (C_3-C_7 cycloalkyl)CH_2; (phenyl)C_1-C_2 alkylene; (pyridyl)C_1-C_2 alkylene; C_5-C_6 cycloalkyl optionally substituted with HO; C_3-C_5 alkenyl optionally substituted with phenyl; or cyclohexenyl;

Preferably R^1 is C_1-C_6 alkyl. Most preferably it is H or CH_3.

R^1 is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, C_3-C_6 alkenyl or C_3-C_6 alkynyl, said alkyl group being optionally substituted by C_3-C_7 cycloalkyl, C_3-C_7 cycloalkyloxy, OH, C_1-C_6 alkoxy, $CONR^3R^4$, $SO_2NR^3R^4$, COR^5, SOR^5, SO_2R^5, CO_2R^6, aryl, aryloxy, aryl(C_1-C_6)alkoxy or heteroaryl, said alkenyl group being optionally substituted by aryl and said cycloalkyl group being optionally substituted by OH; the cycloalkyl and cycloalkenyl groups being optionally linked to the N-atom by a C_1-C_2 alkylene moiety;

R^2 is COR^7, CO_2R^7, SOR^7, SO_2R^7, $CONR^3R^4$, $SO_2NR^3R^4$, $NHCOR^7$, $NHCONR^3R^4$, $NHSO_2R^7$, $NHSO_2NR^3R^4$, OH or CN;

R^3 and R^4 are either each independently selected from H, C_3-C_7 cycloalkyl and C_1-C_6 alkyl, said alkyl group being optionally substituted by C_3-C_7 cycloalkyl or aryl, or R^3 and R^4 taken together represent C_3-C_6 alkylene optionally interrupted by 0, $S(O)_n$, NH or N(C_1-C_6 alkyl);

R^5 is C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkyl(C_1-C_6)alkylene, aryl(C_1-C_6)alkylene, or aryl;

R^6 is C_1-C_6 alkyl, C_3-C_7 cycloalkyl or aryl(C_1-C_6)alkylene;

R^7 is C_1-C_6 alkyl;

X is a direct link or C_1-C_7 alkylene;

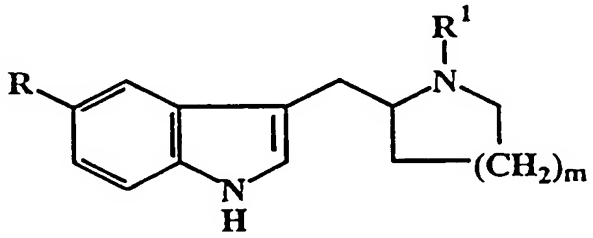
m is 1 or 2; and

INDOLE DERIVATIVES AS 5-HT1-LIKE AGONISTS

The present invention relates to indole derivatives which act on 5-hydroxytryptamine (5-HT) receptors.

More particularly the present invention relates to 3,5-disubstituted indoles which are selective agonists at the "5-HT_1-like" subtype of the 5-hydroxytryptamine receptor. Such "5-HT_1-like" receptors are present in the carotid vascular bed and their activation causes vasoconstriction with a consequent reduction in carotid blood flow. Compounds which have "5-HT_1-like" agonist activity are therefore useful in the treatment of medical conditions which are thought to result from excessive dilation of the carotid bed such as migraine, cluster headache, chronic paroxysmal hemicrania and headache associated with vascular disorders. Certain compounds of the present invention are also agonists at central 5-HT_1 receptors and are therefore useful for the treatment of depression, anxiety, eating disorders, obesity and drug abuse.

The present invention provides compounds of the formula:-



...(I)

and pharmaceutically acceptable salts thereof,

wherein R is phenyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, furyl or thienyl, all of which may be optionally substituted by halo, C_1-C_4 alkyl, C_1-C_4 alkoxy or a group of the formula:-

$$-X-R^2 \ ;$$

^{1}H-N.M.R. ($CDCl_3$) (consistent with the compound existing as a mixture of two rotamers): δ = 1.63-1.90(m,4H), 2.60-2.82(m,1H), 3.10-3.28 (m,1H), 3.30-3.54(m,2H), 4.18(m,1H), 5.15-5.25(m,2H), 5.30(s,1/5H), 6.90 and 6.95 (s,s,1H), 7.05-7.50(m,7H), 7.70 and 7.85(s,s,1H), 8.25(bs,1H).

PREPARATION 36

5-Bromo-3-(1-methylpyrrolidin-2(R)-ylmethyl)-1H-indole

A solution of 3-(1-benzyloxycarbonylpyrrolidin-2(R)-ylcarbonyl)-5-bromo-1H-indole (1.04 g) (see Preparation 35) in dry tetrahydrofuran (20 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (0.27 g) in dry tetrahydrofuran (15 ml) at room temperature under an atmosphere of dry nitrogen. The mixture was heated under reflux with stirring for 18 hours and then cooled. Additional lithium aluminium hydride (50 mg) was added and the mixture heated under reflux for an additional 3 hours. The mixture was again cooled, lithium aluminium hydride (40 mg) was added and the mixture heated under reflux for a further 18 hours. The mixture was cooled, water (0.44 ml) was carefully added with stirring followed by 20% aqueous sodium hydroxide (0.44 ml) and then more water (1.33 ml). The mixture was diluted with ethyl acetate and filtered through a cellulose-based filter aid. The filtrate was washed with water then brine and dried (Na_2SO_4). Evaporation of the solvent gave an oil which was chromatographed on silica gel. Elution with dichloromethane/ethanol/concentrated aqueous ammonia (90:10:0.5) gave, after combination and evaporation of the appropriate fractions, the title compound as a solid, (0.51 g). A small sample was crystallised from dichloromethane/hexane, m.p. 137-140°C. Found: C, 56.65; H, 5.69; N, 9.23; $C_{14}H_{17}N_2Br.0.25\ H_2O$ requires: C, 56.48; H, 5.93; N, 9.41%.

^{1}H-NMR (DMSO-d_6): δ = 1.38-1.73 (m, 4H), 2.09 (dd, J=8.7 and 17.3 Hz, 1H), 2.33 (s, 3H), 2.26-2.36 (m, 1H), 2.47 (dd, J=9.2 and 14.0 Hz, 1H), 2.94-3.03 (m,2H), 7.16 (dd, J= 1.8 and 8.6 Hz, 1H), 7.21 (br d, 1H), 7.31 (d, J=8.6 Hz, 1H), 7.65 (br d, 1H), 11.05 (br s, 1H) ppm.
$[\alpha]_D^{25}$ = +62° (c = 0.10 in methanol).

PREPARATION 37

3-(1-Benzyloxycarbonylpyrrolidin-2(R)-ylmethyl)-5-(3-N,N-dimethylcarbamoylphenyl)-1H-indole

A mixture of 3-N,N-dimethylcarbamoylphenyltri-n-butylstannane (see Preparation 13) (1.315g, 3.00mmol), tri-o-tolylphosphine (240mg, 0.788mmol), palladium (II) acetate (30mg, 0.134mmol), triethylamine (0.80ml, 5.74mmol) and 3-(1-benzyloxycarbonylpyrrolidin-2(R)-ylmethyl)-5-bromo-1H-indole (1.124g, 2.72mmol) (see Preparation 35B) were reacted together using a procedure similar to that described for Example 1. This yielded the title compound as a pale yellow foam (482mg).
Found: C,72.47; H,6.21; N,8.10; $C_{30}H_{31}N_3O_3.\frac{1}{4}CH_2Cl_2$ requires: C,72.26; H,6.31; N,8.36%.
$[\alpha]_D^{25}$ = -28° (c = 0.1 in methanol).

^{1}H-N.M.R. ($CDCl_3$) (consistent with the compound existing as two rotamers): δ = 1.60-2.00(m,4H), 2.70-2.90(m,1H), 2.90-3.55(m,8H), 4.20-4.30(m,1H), 5.10-5.30(m,2H), 5.30(s,½H), 6.95, 7.10(s,s,1H), 7.15-7.30(m, integral obscured by solvent), 7.30-7.50(m,8H), 7.50-7.75(m,2H), 7.80, 7.95(s,s,1H), 8.25(s,1H).

PREPARATION 38

3-(1-Benzyloxycarbonylpyrrolidin-2(R)-ylmethyl)-5-(3-hydroxymethylphenyl)-1H-indole

3-Hydroxymethylphenyltri-n-butylstannane (2.016g, 5.076mmol) (see Preparation 25) and 3-(1-benzyloxycarbonylpyrrolidin-2(R)-ylmethyl)-5-bromo-1H-indole (1.902g, 4.602mmol) (see Preparation 35B) were reacted together in the presence of tri-o-tolylphosphine, triethylamine and palladium (II) acetate using a procedure similar to that described in Example 1. This yielded the title compound as a white foam (1.050g).
Found: C,75.58; H,6.51; N,5.88; $C_{28}H_{28}N_2O_3.1/12CH_2Cl_2$ requires: C,75.36; H,6.34; N,6.26%.
$[\alpha]_D^{25}$ = -22° (c = 0.1 in methanol).

^{1}H-N.M.R. ($CDCl_3$) (consistent with the compound existing as two rotamers): δ = 1.65-2.00(m,4H), 2.50(s,1H), 2.80-2.90(m,1H), 3.15-3.30(m,1H), 3.30-3.55(m,2H), 4.20-4.30(m,1H), 4.70-4.80(m,1H), 5.10-5.30(m,2 1/6H), 6.95, 7.00(s,s,1H), 7.00-7.70(m, integral obscured by solvent), 7.80, 8.00(s,s,1H), 8.10(s,1H).

PREPARATION 39

3-(1-Benzyloxycarbonylpyrrolidin-2(R)-ylmethyl)-5-(4-hydroxymethylphenyl)-1H-indole

4-Hydroxymethylphenyltri-n-butylstannane (1.008g, 2.538mmol) (see Preparation 24) and 3-(1-benzyloxycarbonylpyrrolidin-2(R)-ylmethyl)-5-bromo-1H-indole (0.951g, 2.301mmol) (see Preparation 35B) were reacted together in the presence of tri-o-tolylphosphine, triethylamine and palladium (II) acetate using a procedure similar to that described in Example 1. This yielded the title compound as a white foam (450mg).

Found: C,74.61; H,6.49; N,5.63; $C_{28}H_{28}N_2O_3.3/20$ $CH_3CH_2OCOCH_3.1/10CH_2Cl_2$ requires: C,74.57; H,6.43; N,6.02%.

^{1}H-N.M.R. ($CDCl_3$) (consistent with the compound existing as two rotamers): δ = 1.30(t,3/10H), 1.45-2.00(m,4 9/20H), 2.65-2.95(m,1H), 3.15-3.55(m, 3 9/20H), 4.15-4.35(m,1H), 4.70(bs,2H), 5.10-5.30 (m, 2 1/5H), 6.90, 7.00(s,s,1H), 7.05-7.75(m, integral obscured by solvent), 7.80, 7.95(s,s,1H), 8.25.

PREPARATION 40

3-(1-Benzyloxycarbonylpyrrolidin-2(R)-ylmethyl)-5-(3-carbamoylphenyl)-1H-indole

3-carbamoylphenyltri-n-butylstannane (3.076g, 7.50mmol) (see Preparation 9) and 3-(1-benzyloxycarbonylpyrrolidin-2(R)-ylmethyl)-5-bromo-1H-indole (2.81g, 6.80mmol) (see Preparation 35B) were reacted together in the presence of tri-o-tolylphosphine, triethylamine and palladium (II) acetate using a procedure similar to that described in Example 1. This yielded the title compound as a pale yellow foam (954mg). Found: C,68.45; H,5.92; N,8.10; $C_{28}H_{27}N_3O_3.7/12CH_2Cl_2$ requires: C,68.24; H,5.64; N,8.35%.

^{1}H-N.M.R. ($CDCl_3$) (consistent with the compound existing as two rotamers): δ = 1.50-2.05(m,4H), 2.65-3.00(m,1H), 3.00-3.20(m,1H), 3.20-3.50(m,2H), 4.30-4.40(m,1H), 5.00-5.30(m,4 1/6H), 5.40-5.80(bs,1H), 7.00-8.10(m, integral obscured by solvent), 8.15, 8.25(s,s,1H), 8.20, 8.30(s,s,1H).

PREPARATION 41

3-(1-Benzyloxycarbonylpyrrolidin-2(R)-ylmethyl)-5-(4-carbamoylphenyl)-1H-indole

4-carbamoylphenyltri-n-butylstannane (1.833g, 4.469mmol) (see Preparation 8) and 3-(1-benzyloxycarbonylpyrrolidin-2(R)-ylmethyl)-5-bromo-1H-indole (1.67g, 4.05mmol) (see Preparation 35B) were reacted together in the presence of tri-o-tolylphosphine, triethylamine and palladium (II) acetate using a procedure similar to that described in Example 1. This yielded the title compound as an off-white foam (541mg). Found: C,71.64; H,6.02; N,8.57; $C_{28}H_{27}N_3O_3.¼CH_2Cl_2$ requires: C,71.84; H,5.84; N,8.85%.

^{1}H-N.M.R. ($CDCl_3$) (consistent with the compound existing as two rotamers): δ = 1.65-1.90(m,4H), 2.60-2.90(m,1H), 3.20-3.50(m,3H), 4.20-4.30(m,1H), 5.00-5.30(m,2½H), 5.55(bs,1H), 6.10(bs,1H), 7.00, 7.05(s,s,1H), 7.15-7.50(m, integral obscured by solvent), 7.60, 7.70(d,d,2H), 8.00-7.90(m,3H), 8.10(s,1H).

PREPARATION 42

5-Methoxycarbonyl-3-pyridyltri-n-butylstannane

3-Bromo-5-methoxycarbonylpyridine was reacted with hexa(n-butyl)distannane in the presence of tri-o-tolylphosphine, triethylamine and palladium (II) acetate using a procedure similar to that described in Preparation 1. The product, which was impure, was used without characterisation in the preparation of Example 48.

PREPARATION 43

5-Carbamoyl-3-pyridyltri-n-butylstannane

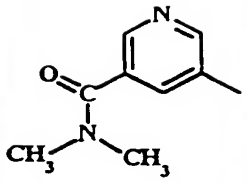
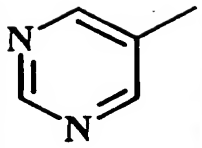
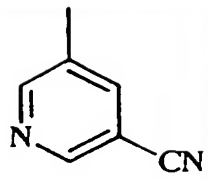
3-Bromo-5-carbamoylpyridine was reacted with hexa(n-butyl)distannane in the presence of tri-o-tolylphosphine, triethylamine and palladium (II) acetate using a procedure similar to that described in Preparation 1. This yielded the title compound. Found: C,52.30; H,7.59; N,6.52; $C_{18}H_{32}N_2OSn$ requires: C,52.58; H,7.85; N,6.81.

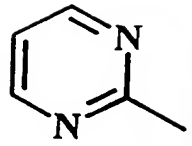
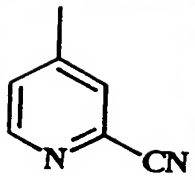
^{1}H-N.M.R. (d_6-DMSO): δ = 0.85(t,9H), 1.10(t,6H), 1.15-1.35(m,6H), 1.45-1.60(m,6H), 7.55(bs,1H), 8.15(bs,1H), 8.20(s,1H), 8.65(s,1H), 8.60(s,1H), 8.90(s,1H).

PREPARATIONS 44 to 48

The stannane derivatives of the following tabulated preparations were prepared by similar methods to that of Preparation 1 using the appropriate bromoheteroaromatic starting materials, and they have the following general formula:-

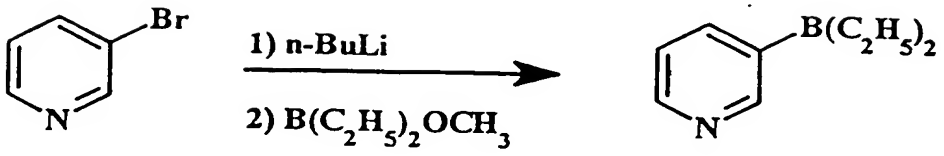
$$RSn[(CH_2)_3CH_3]_3$$

Prep No	R	Analysis (%)	^{1}H-NMR ($CDCl_3$)
44		-	δ = 0.90(t,9H), 1.10 (t,6H), 1.25-1.40 (m,6H), 1.45-1.60 (m,6H), 3.00(s,3H), 3.15(s,3H), 7.80 (s,1H), 8.55(s,1H), 8.60(s,1H).
45		-	δ = 0.90(t,9H), 1.15 (t,6H), 1.30-1.40 (m,6H), 1.45-1.60 (m,6H), 8.65(s,2H), 9.10(s,1H).
46		-	δ = 0.85(t,9H), 1.10 (t,6H), 1.20-1.40 (m,6H), 1.40-1.65 (m,6H), 7.95(s,1H), 8.95(s,s,2H).

Prep No	R	Analysis (%)	^{1}H-NMR ($CDCl_3$)
47		-	δ = 0.85(t,9H), 1.15 (t,6H), 1.25-1.40 (m,6H), 1.45-1.65 (m,6H), 7.10(dd,1H), 8.65(d,2H).
48		-	δ = 0.85(t,9H), 1.15 (t,6H), 1.20-1.45(m,6H), 1.45-1.70 (m,6H), 7.55(d,1H), 7.75(s,1H), 8.55 (d,1H).

PREPARATION 49

Diethyl(3-pyridyl)borane

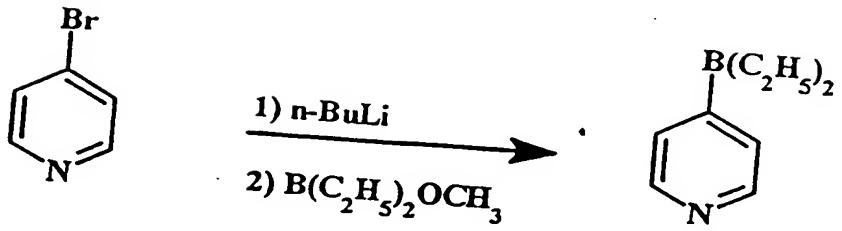


n-Butyllithium (25.6ml of a 2.5M solution in hexanes, 64mmol) was added as a rapid stream of droplets to a solution of 3-bromopyridine (10.04g, 64mmol) in ether (200ml) at -40°C, under nitrogen. The addition was carried out over 5 minutes and the reaction temperature was maintained below -40°C throughout. The reaction was stirred at -40°C for 20 minutes and then cooled to -70°C whereupon diethylmethoxyborane in tetrahydrofuran (64.0ml of a 1M solution, 64mmol) was added as a rapid stream of droplets over 5 minutes. The reaction temperature was maintained below -63°C throughout this addition. The reaction was then allowed to warm slowly to room temperature whereupon it was diluted with ethylacetate and washed with brine. The organic layer was dried (Na_2SO_4) and the solvent removed under reduced pressure to give the crude product. This was purified by column chromatography on silica gel, eluting with dichloromethane to afford, after combination and evaporation of the appropriate fractions, the title compound as a yellow crystalline solid (7.3g). Found: C,73.40; H,9.53; N,8.92; $C_9H_{14}NB$ requires: C,73.52; H,9.60; N,9.53%.

^{1}H-N.M.R. ($CDCl_3$): δ = 0.40(t,6H), 0.50-0.75(m,4H), 7.15-7.30(m, integral obscured by solvent), 7.55(s,1H), 7.70(d,1H), 8.00(d,1H).

PREPARATION 50

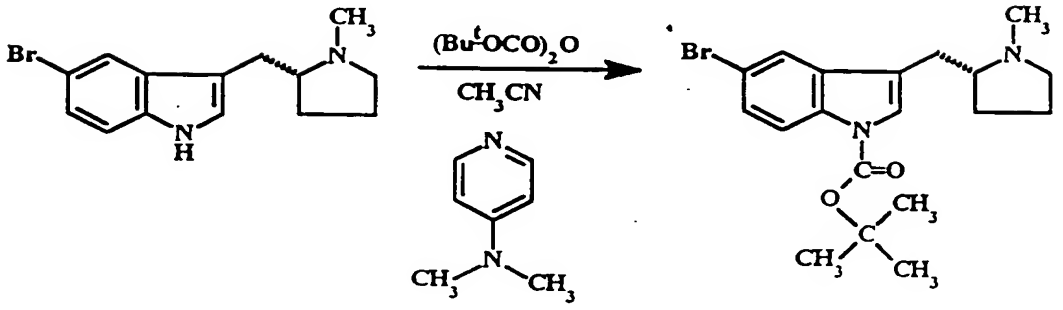
Diethyl(4-pyridyl)borane



4-Bromopyridine was reacted with n-butyllithium and then with diethylmethoxyborane using a procedure similar to that in Preparation 49. This gave the title compound, which was used without characterisation.

PREPARATION 51

5-Bromo-1-(t-butoxycarbonyl)-3-(1-methylpyrrolidin-2(R)-ylmethyl)-indole

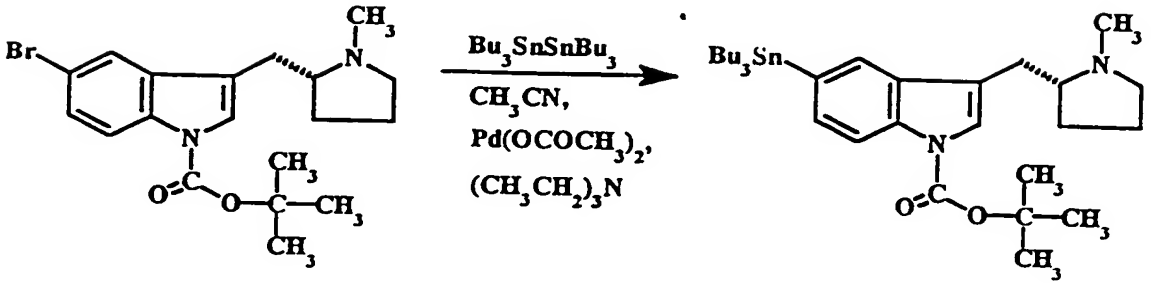


To a stirred solution of 5-bromo-3-(1-methylpyrrolidin-2(R)-ylmethyl)-1H-indole (199mg, 0.68mmol) (see Preparation 36) in acetonitrile (4.0ml) under nitrogen was added a solution of di-t-butyldicarbonate (296mg, 1.36mmol) in acetonitrile (1.0ml). 4-N,N-Dimethylaminopyridine (83mg, 0.68mmol) was then added in one portion. The reaction was stirred for 16 hours at room temperature whereupon the solvent was removed under reduced pressure to give the crude product. This was purified by column chromatography on silica gel to afford, after combination of the appropriate fractions, the title compound (240mg). Found: C,56.37; H,6.38; N,6.74; $C_{19}H_{25}N_2O_2Br.3/16CH_2Cl_2$ requires C,56.31; H,6.25; N,6.85%.

^{1}H-N.M.R. ($CDCl_3$): δ = 1.65(s,9H), 1.40-1.90(m,4H), 2.15-2.30(m,1H), 2.45(s,3H), 2.35-2.55(m,2H), 2.95-3.17(m,2H), 5.30(s,3/8H), 7.15-7.20 (m,2H), 7.65(s,1H), 7.95(bs,1H).

PREPARATION 52

1-(t-butoxycarbonyl)-3-(1-methylpyrrolidin-2(R)-ylmethyl)-5-(tri-n-butylstannyl)-indole

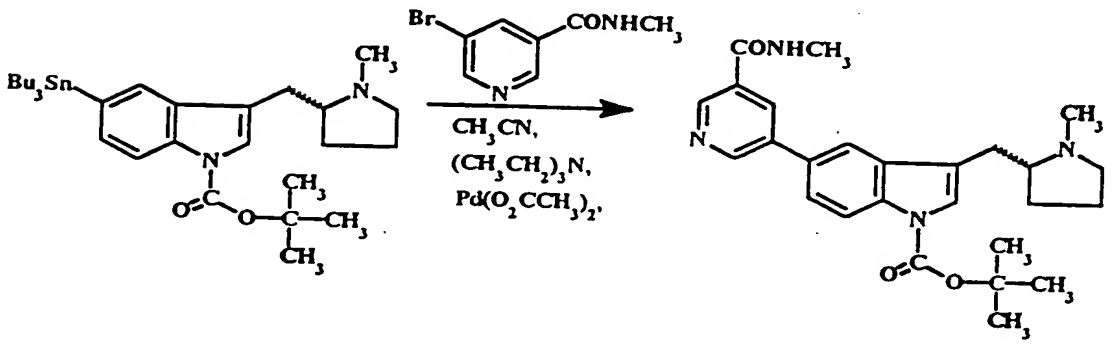


5-Bromo-1-(t-butyloxycarbonyl)-3-(1-methylpyrrolidin-2(R)-ylmethyl)-indole (see Preparation 51) was reacted with hexa(n-butyl)distannane in the presence of tri-o-tolyphosphine, triethylamine and palladium (II) acetate using a procedure similar to that described in Preparation 1. This yielded the title compound.

^{1}H-N.M.R. ($CDCl_3$): δ = 0.85(t,9H), 1.10(t,6H), 1.15-1.40(m,6H), 1.40-1.95(m,10H), 1.65(s,9H), 2.15-2.30(m,1H), 2.50(s,3H), 2.40-2.65 (m,2H), 3.05-3.40(m,2H), 7.30-7.45(m,2H), 7.60(s,1H), 8.05(bs,1H).

PREPARATION 53

1-(t-butoxycarbonyl)-5-(5-N-methylcarbamoyl-3-pyridyl)-3-(1-methylpyrrolidin-2(R)-ylmethyl)-indole

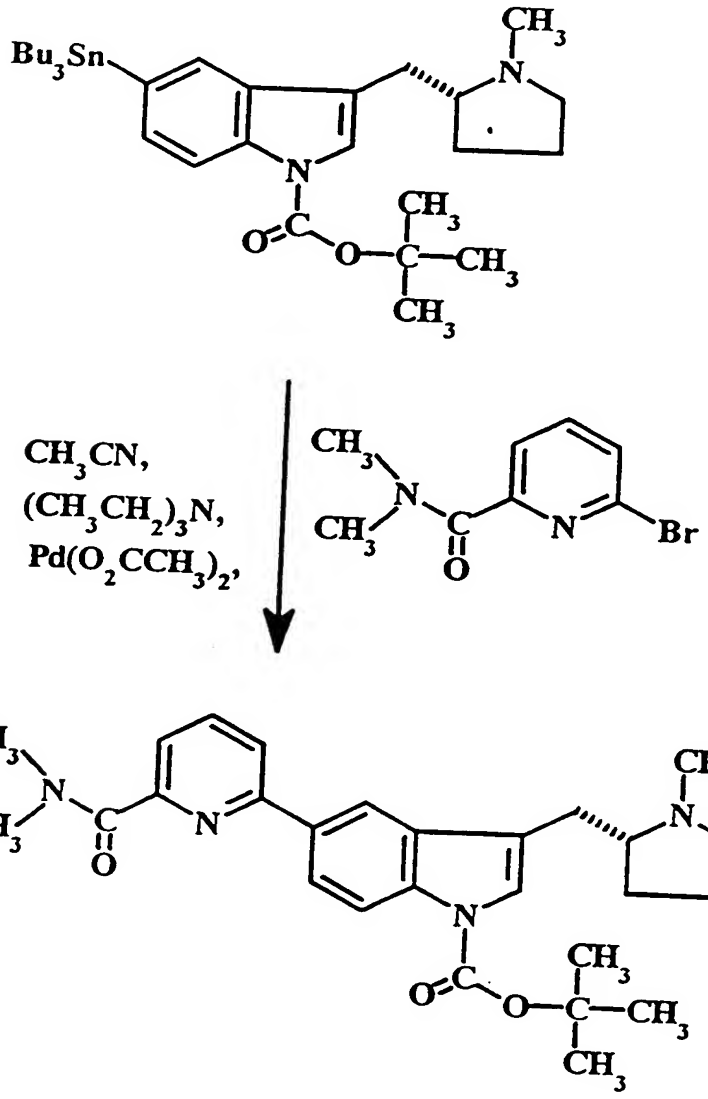


1-(t-Butoxycarbonyl)-3-(1-methylpyrrolidin-2(R)-ylmethyl)-5-(tri-n-butylstannyl)-indole (see Preparation 52) was reacted with 3-bromo-5-(N-methylcarbamoyl)pyridine in the presence of tri-o-tolylphosphine, triethylamine and palladium (II) acetate using a procedure similar to that described in Example 1. This yielded the title compound. Found: C,66.88; H,6.42; N,11.69; $C_{28}H_{32}N_4O_3.7/24CH_2Cl_2$ requires: C,66.71; H,6.94; N,11.84%.

^{1}H-N.M.R. ($CDCl_3$): δ = 1.55-1.95(m,4H), 2.20-2.35(m,1H), 2.45(s,3H), 2.40-2.60(m,1H), 2.65-2.75(m,1H), 3.10(s,s,3H), 3.10-3.30(m,2H), 5.30(s,7/12H), 6.37(bs,1H), 7.10(s,1H), 7.40-7.50(m,2H), 7.85(s,1H), 8.20(s,1H), 8.37(s,1H), 8.87(s,1H), 9.00(s,1H).

PREPARATION 54

1-(t-butoxycarbonyl)-5-(6-N,N-dimethylcarbamoyl-2-pyridyl)-3-(1-methylpyrrolidin-2(R)-ylmethyl)-indole



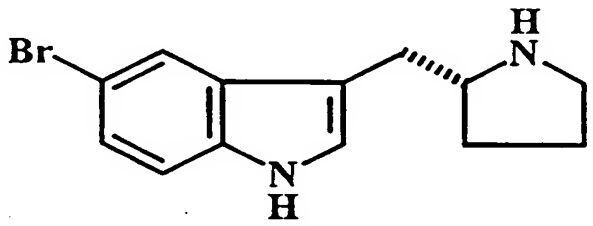
1-(t-Butoxycarbonyl)-3-(1-methylpyrrolidin-2(R)-ylmethyl)-5-(tri-n-butylstannyl)-indole (see Preparation 52) was reacted with 2-bromo-6-(N,N-dimethylcarbamoyl)pyridine in the presence of tri-o-tolylphosphine, triethylamine and palladium (II) acetate using a procedure similar to

that described in Example 1. This yielded the title compound. Found: C,68.94; H,7.28; N,11.46; $C_{27}H_{34}N_4O_3.1/8CH_2Cl_2$ requires: C,68.85; H,7.30; N,11.84%.

^{1}H-N.M.R. ($CDCl_3$): δ = 1.45-1.95(m,4H), 1.65(s,9H), 2.17-2.30(m,1H), 2.47(s,3H), 2.50-2.70(m,2H), 3.10-3.30(m,2H), 3.20(s,3H), 3.25(s,3H), 5.30(s,¼H), 7.40(s,1H), 7.60(d,1H), 7.75-7.90(m,2H), 7.95(d,1H), 8.15-8.25(m,2H).

PREPARATION 55

5-Bromo-3-(pyrrolidin-2(R)-ylmethyl)-1H-indole



A) To 3-(1-benzyloxycarbonylpyrrolidin-2(R)-ylmethyl)-5-bromo-1H-indole (see Preparation 35B) (10.0g, 24.2mmol) was added dropwise hydrogen bromide/acetic acid (36% w/w) (17ml) at 0°C, with stirring. After 50 minutes at 0°C the solvent was removed by evaporation under reduced pressure, and the residue azeotroped with toluene. The resulting oil was partitioned between dichloromethane and 2M aqueous sodium carbonate. The separated aqueous phase was re-extracted with dichloromethane and the combined organic phases dried (Na_2SO_4) and evaporated

under reduced pressure. Purification by column chromatography on silica gel, eluting with a gradient of dichloromethane: methanol:0.88 aqueous ammonia (95:5:0 to 95:5:2), yielded the title compound as an oil (2.01g). Found: C,54.75; H,5.41; N,9.63. $C_{13}H_{16}BrN_2.1/5CH_2Cl_2$ requires: C,54.84; H,5.37; N,9.67%.

$[\alpha]_D^{25}$ = -9° (c = 0.1 in methanol).

^{1}H-N.M.R. ($CDCl_3$): δ = 1.35-1.50(m,1H), 1.68-1.98(m,3H), 2.45(bs,1H), 2.72-2.92(m,3H), 2.96-3.08(m,1H), 3.28-3.43(m,1H), 5.28(s,2/5H), 7.06(s,1H), 7.18-7.26(m,2H), 7.72(s,1H), 8.52(bs,1H).

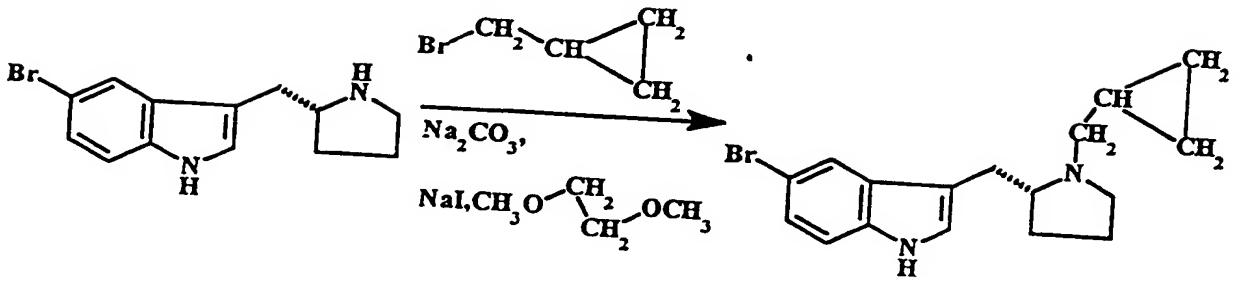
Alternatively the title compound was prepared by the following procedure:

B) 3-(1-Benzyloxycarbonylpyrrolidin-2(R)-ylmethyl)-5-bromo-1H-indole (see Preparation 35B) (5.00g, 12.10mmol) was dissolved in dichloromethane and the resulting solution was added dropwise to a stirred mixture of boron-trifluoride.etherate (17.15g, 14.9ml, 12.1mmol) and ethane thiol (21.4g, 25.5ml, 344mmol) at room temperature under nitrogen. After 68 hours the reaction mixture was added by pipette to a 10% aqueous sodium carbonate solution (500ml) and extracted with ethyl acetate (3x400ml). The combined organic extract was dried (Na_2SO_4) and the solvent evaporated under reduced pressure. Purification by column chromatography on silica gel, eluting with dichloromethane: methanol:0.880 aqueous ammonia (90:10:1), yielded the title compound as a foam (2.1g). Found: C,55.04; H,5.29; N,9.83. $C_{13}H_{15}BrN_2.3/50CH_2Cl_2$ requires: C,55.10; H,5.35; N,9.83%. $[\alpha]_D^{25}$ = -12° (c = 0.1 in methanol).

^{1}H-N.M.R. ($CDCl_3$): δ = 1.38-1.50(m,1H), 1.68-1.98(m,3H), 2.32(bs,1H), 2.76-2.90(m,3H), 3.00-3.10(m,1H), 3.32-3.41 (m,1H), 5.30(s,3/25H), 7.06(s,1H), 7.22-7.30(m,2H), 7.75(s,1H), 8.37(bs,1H).

PREPARATION 56

5-Bromo-3-(1-cyclopropylmethylpyrrolidin-2(R)-ylmethyl)-1H-indole



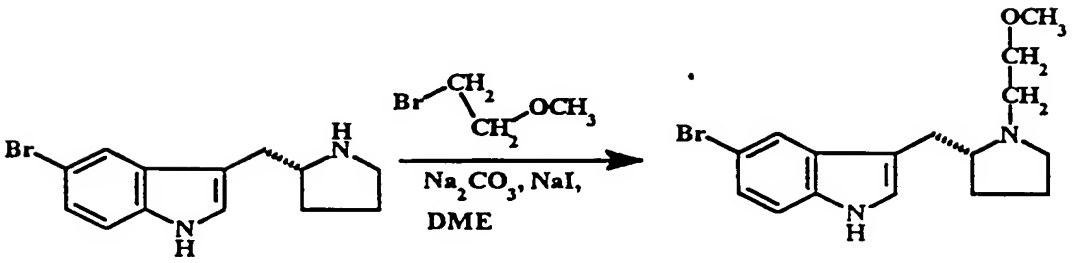
5-Bromo-3-(pyrrolidin-2(R)-ylmethyl)-1H-indole (1.84g, 6.3mmol) (see Preparation 55), cyclopropylmethyl bromide (0.67ml, 6.9mmol), sodium carbonate (0.73g, 6.9mmol) and sodium iodide (1.0g, 6.7mmol) in 1,2-dimethoxyethane (10ml) was refluxed under nitrogen for 14 hours. After cooling to room temperature the reaction mixture was partitioned between ethyl acetate and aqueous sodium carbonate. The organic phase was washed with more aqueous sodium carbonate, dried (Na_2SO_4) and the solvent evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with dichloromethane/methanol/ammonium hydroxide (90:10:0.05) to yield the title compound as a foam (2.09g). Found: C,61.22; H,6.40; N,8.39. $C_{17}H_{21}BrN_2$ requires: C,61.26; H,6.35; N,8.41%.

$[\alpha]_D^{25} = +72°$ (c = 0.1 in methanol).

^{1}H-N.M.R. ($CDCl_3$): δ = 0.12-0.20(m,2H), 0.50-0.58(m,2H), 0.92-1.08(m,1H), 1.50-1.92(m,4H), 1.98-2.08(m,1H), 2.20-2.30(m,1H), 2.55-2.68(m,2H), 2.90-2.98(m,1H), 3.08-3.18(m,1H), 3.38-3.50(m,1H), 7.04(s,1H), 7.20-7.28(m,2H), 7.70(s,1H), 8.10(bs,1H).

PREPARATION 57

5-Bromo-3-[1-(2-methoxyethyl)pyrrolidin-2(R)-ylmethyl]-1H-indole

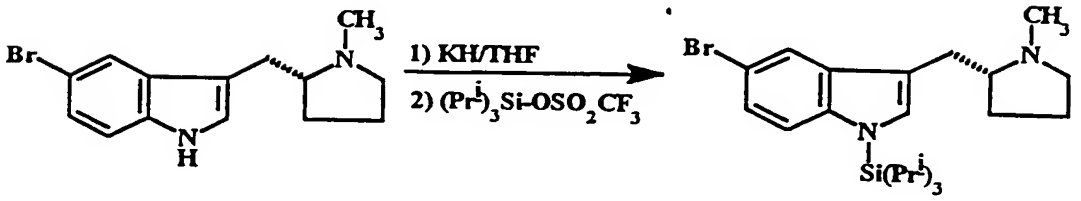


5-Bromo-3-(pyrrolidin-2(R)-ylmethyl)-1H-indole (3.20g, 11.5mmol) (see Preparation 55), 1-bromo-2-methyoxyethane (1.67g, 1.13ml, 12.1mmol), sodium carbonate (1.34g, 12.6mmol) and sodium iodide (1.89g, 12.6mmol) in 1,2-dimethoxyethane (75ml) was refluxed for 16 hours under nitrogen. The reaction mixture was then concentrated under reduced pressure to a volume of about 20ml. The resulting slurry was partitioned between ethyl acetate and aqueous sodium carbonate. The organic phase was dried (Na_2SO_4) and the solvent evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with dichloromethane/methanol/ammonium hydroxide (89:10:1) to yield, after combination and evaporation of the appropriate fractions, the title compound. Found: C,57.25; H,6.41; N,8.14. $C_{16}H_{21}BrN_2O$ requires: C,56.98; H,6.28; N,8.31.

^{1}H-N.M.R. ($CDCl_3$): δ = 1.50-1.85(m,4H), 2.15-2.30(m,1H), 2.40-2.50 (m,1H), 2.50-2.75(m,2H), 3.08-3.15(m,1H), 3.15-3.30(m,2H), 3.40(s,3H), 3.55-3.65(m,2H), 7.03(s,1H), 7.15-7.30(m, integral obscured by solvent), 7.70(s,1H), 8.00(bs,1H).

PREPARATION 58

5-Bromo-3-(1-methylpyrrolidin-2(R)-ylmethyl)-1-triisopropylsilylindole

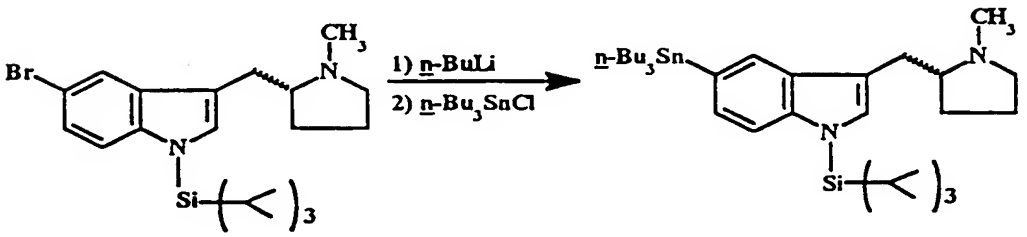


To a suspension of potassium hydride (309mg of a 30% KH suspension in mineral oil, 2.70mmol) in tetrahydrofuran (12.0ml) at 0°C under nitrogen, was added dropwise a solution of 5-bromo-3-(1-methylpyrrolidin-2(R)-ylmethyl)-1H-indole (528mg, 1.80mmol) (see Preparation 36) in tetrahydrofuran (3.0ml). The ice-bath was removed and the reaction allowed to warm to room temperature with stirring, over 30 minutes. The reaction was cooled back down to 0°C and triisopropyltriflate (0.761ml, 2.7mmol) was then added dropwise. The reaction was stirred for a further 30 minutes during which time the solution was allowed to warm to room temperature. The reaction mixture was then partitioned between ethyl acetate and aqueous sodium carbonate. The organic layer was separated and the aqueous phase re-extracted with ethyl acetate. The combined organic phases were dried (Na_2SO_4) and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with ethyl acetate/diethylamine (98:2), to give, after combination and evaporation of the appropriate fractions, the title compound as an oil (670mg). Found: C,62.11; H,8.61; N,6.17. $C_{23}H_{37}N_2BrSi$ requires: C,61.45; H,8.30; N,6.23%.

^{1}H-N.M.R. ($CDCl_3$): δ = 1.10(d,18H), 1.40-1.85(m,7H), 2.18-2.25(m,1H), 2.38-2.60(m,2H), 2.40(s,3H), 3.05-3.20(m,2H), 7.00(s,1H), 7.20(d,1H), 7.30(d,1H), 7.62(s,1H).

PREPARATION 59

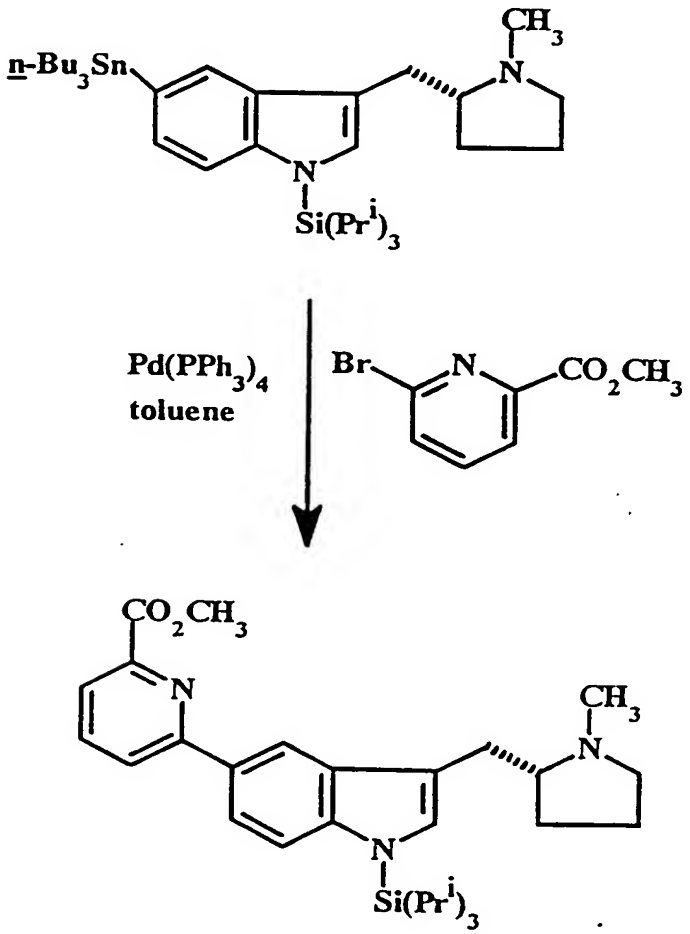
3-(1-methylpyrrolidin-2(R)-ylmethyl)-5-(tri-n-butylstannyl)-1-triisopropylsilylindole



n-ButylLithium (7.80ml of a 2.5M solution in hexanes, 19.49ml) was added dropwise to a solution of 5-bromo-3-(1-methylpyrrolidin-2(R)-ylmethyl)-1-triisopropylsilylindole (6.28g, 13.97mmol) (Preparation 58) in tetrahydrofuran (430ml) at -78°C. The reaction was then stirred at -70°C for ½ hour whereupon tri-n-butylstannylchloride (3.97ml, 14.64mmol) was added and the reaction stirred at -70°C for 20 minutes. The reaction was then warmed to room temperature and 14.4ml of water was added and the resulting solution partitioned (97½:2½) to afford, after combination and evaporation of the appropriate fractions, the title compound as an oil. Found: C,70.29; H,8.72; N,8.17. $C_{30}H_{43}N_3O_2Si.1/8CH_2Cl_2$ requires: C,70.07; H,8.44; N,8.14%. ^{1}H-N.M.R. ($CDCl_3$): δ = 1.10(d,18H), 1.52-1.90(m,7H), 2.18-2.28(m,1H), 2.40-2.55(m,1H), 2.50(s,3H), 2.60-2.75(m,1H), 3.08-3.30(m,2H), 4.02(s,3H), 5.25(s,¼H), 7.10(s,1H), 7.55(d,1H), 7.80-8.02(m,4H), 8.20(s,1H).

PREPARATION 60

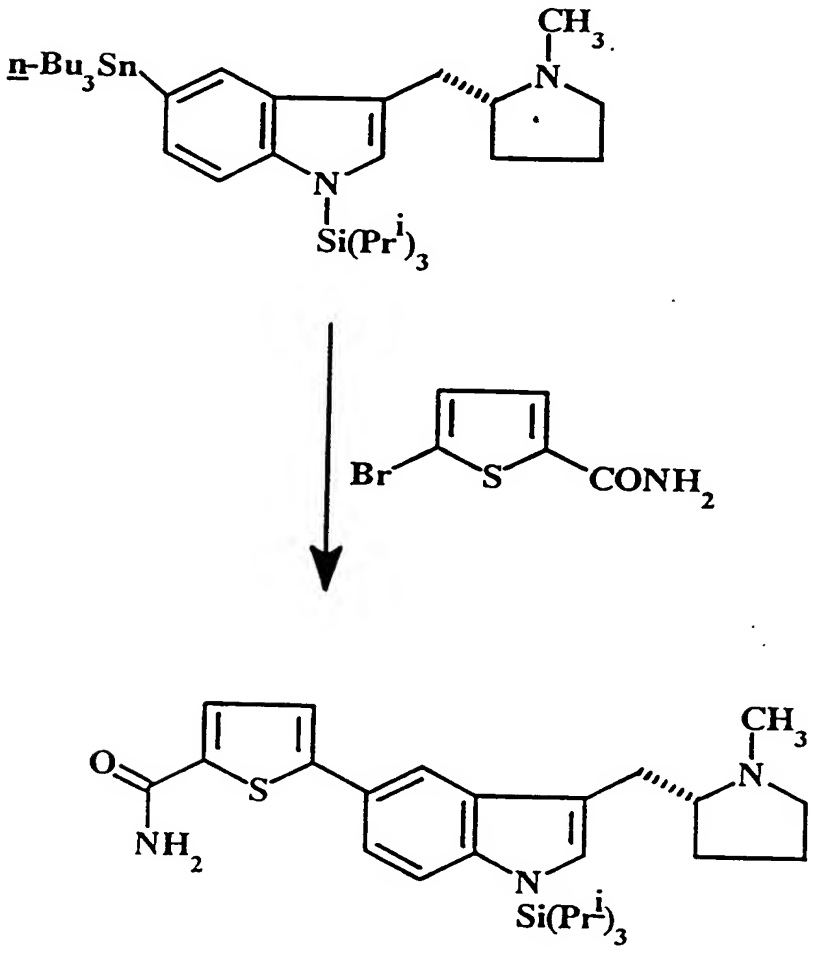
5-(6-Methoxycarbonyl-2-pyridyl)-3-(1-methylpyrrolidin-2(R)-ylmethyl)-1-triisopropylsilylindole



3-(1-methylpyrrolidin-2(R)-ylmethyl)-5-(tri-n-butylstannyl)-1-triisopropylsilylindole (500mg, 0.910mmol) (see Preparation 59), 2-bromo-6-methoxycarbonylpyridine (197mg, 0.910mmol) and tetrakistriphenylphosphinepalladium(O) ($Pd(PPh_3)_4$) were reacted in refluxing toluene (8.0ml), under nitrogen, for 16 hours. The solvent was then removed under reduced pressure and the residue purified by column chromatography on silica gel, eluting with ethyl acetate/diethylamine between aqueous sodium carbonate and ethyl acetate. The organic layer was dried (Na_2SO_4) and the solvent removed under reduced pressure. The residue was purified by column chromatography, eluting with dichloromethane:methanol:ammonium hydroxide (94.5:5:0.5) to give the title compound as a viscous oil. Found: C,63.90; H,9.56; N,4.13. $C_{35}H_{64}N_2SiSn$ requires: C,63.72; H,9.78; N,4.25%.
^{1}H-N.M.R. ($CDCl_3$): δ = 0.90(t,9H), 1.00-1.20(m,24H), 1.40-1.90(m,13H), 2.15-2.30(m,1H), 2.48(s,3H), 2.40-2.70(m,2H), 3.15-3.30(m,2H), 7.00(s,1H), 7.20(d,1H), 7.45(d,1H), 7.65(s,1H).

PREPARATION 61

5-(5-Carbamoyl-2-thienyl)-3-(1-methylpyrrolidin-2(R)-ylmethyl)-1-triisopropylsilylindole

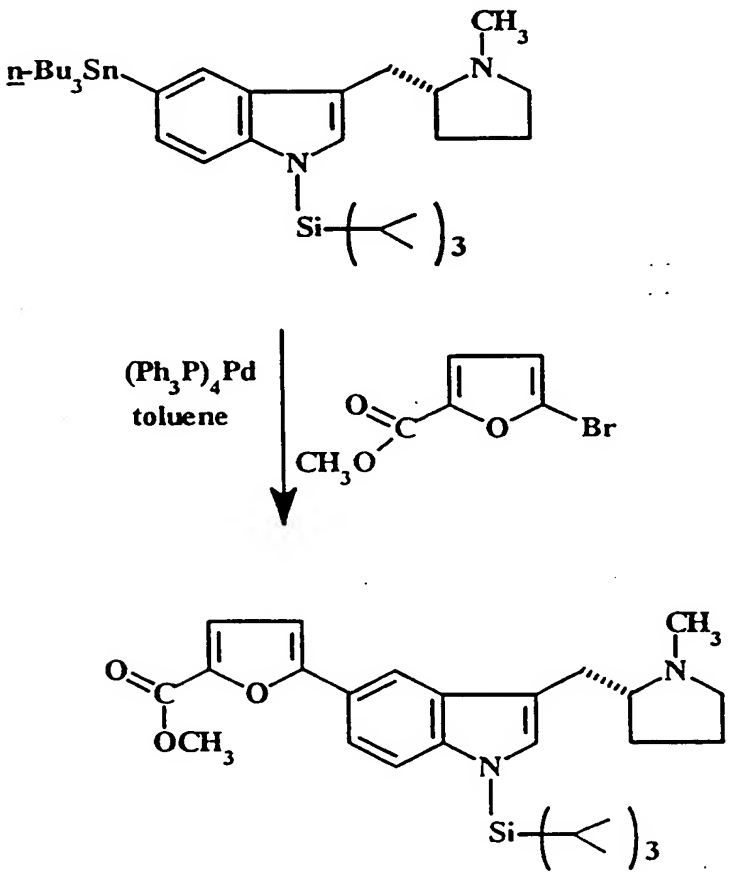


3-(1-methylpyrrolidin-2(R)-ylmethyl)-5-(tri-n-butylstannyl)-1-triisopropylsilylindole (see Preparation 59) was reacted with 2-bromo-5-carbamoylthiophene in the presence of tetrakistriphenylphosphinepalladium (0), in toluene, using a procedure similar to that described in Preparation 60. This gave the title compound. Found: C,65.18; H,8.10; N,8.24. $C_{28}H_{41}N_3OSSi.5/16CH_2Cl_2$ requires: C,65.10; H,8.03; N,8.04%.

^{1}H-N.M.R. ($CDCl_3$): δ = 1.10(d,18H), 1.45-1.90(m,7H), 2.25-2.35(m,1H), 2.55(s,3H), 2.50-2.70(m,2H), 3.15-3.30(m,2H), 5.30(s,5/8H), 7.10(s,1H), 7.25-7.30(m, integral obscured by solvent), 7.40-7.55(m,3H), 7.85(s,1H).

PREPARATION 62

5-(5-Methoxycarbonyl-2-furyl)-3-(1-methylpyrrolidin-2(R)-ylmethyl)-1-triisopropylsilylindole

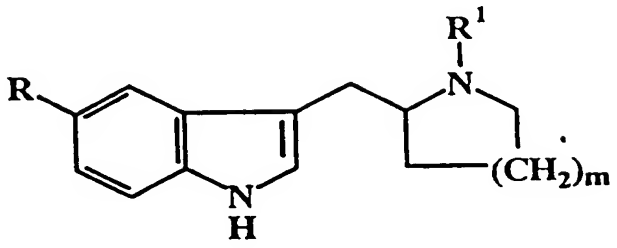


3-(1-methylpyrrolidin-2(R)-ylmethyl)-5-(tri-n-butylstannyl)-1-triisopropylsilylindole (see Preparation 59) was reacted with 2-bromo-5-methoxycarbonylfuran in the presence of tetrakistriphenylphosphinepalladium(O), in toluene, using a procedure similar to that described in Preparation 60. This gave the title compound. Found: C,68.21; H,8.55; N,5.84. $C_{29}H_{42}N_2O_3Si.5/24CH_2Cl_2$ requires: C,68.46; H,8.34; N,5.47%.

^{1}H-N.M.R.: δ = 1.10(d,18H), 1.40-1.85(m,7H), 2.15-2.25(m,1H), 2.50(s,3H), 2.50-2.70(m,2H), 3.05-3.40(m,2H), 3.95(s,3H), 5.30(s,5/12H), 6.70(d,1H), 7.10(s,1H), 7.15-7.25(m, integral obscured by solvent), 7.50(d,1H), 7.60(d,1H), 8.00(s,1H).

CLAIMS

1. A compound of formula (I):



...(I)

or a pharmaceutically acceptable salt thereof,

wherein R is phenyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, furyl or thienyl, all of which may be optionally substituted by halo, C_1-C_4 alkyl, C_1-C_4 alkoxy or a group of the formula:-

$-X-R^2$;

R^1 is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, C_3-C_6 alkenyl or C_3-C_6 alkynyl, said alkyl group being optionally substituted by C_3-C_7 cycloalkyl, C_3-C_7 cycloalkyloxy, OH, C_1-C_6 alkoxy, $CONR^3R^4$, $SO_2NR^3R^4$, COR^5, SOR^5, SO_2R^5, CO_2R^6, aryl, aryloxy, aryl(C_1-C_6)alkoxy or heteroaryl, said alkenyl group being optionally substituted by aryl and said cycloalkyl group being optionally substituted by OH; the cycloalkyl and cycloalkenyl groups of the foregoing groups being optionally linked to the N-atom by a C_1-C_2 alkylene moiety;

R^2 is COR^7, CO_2R^7, SOR^7, SO_2R^7, $CONR^3R^4$, $SO_2NR^3R^4$, $NHCOR^7$, $NHCONR^3R^4$, $NHSO_2R^7$, $NHSO_2NR^3R^4$, OH or CN,

R^3 and R^4 are either each independently selected from H, C_3-C_7 cycloalkyl and C_1-C_6 alkyl, said alkyl group being optionally substituted by C_3-C_7 cycloalkyl or aryl,
or R^3 and R^4 taken together represent C_3-C_6 alkylene optionally interrupted by O, $S(O)_n$, NH or N(C_1-C_6 alkyl);

R^5 is C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkyl(C_1-C_6)alkylene, aryl(C_1-C_6)alkylene or aryl;

R^6 is C_1-C_6 alkyl, C_3-C_7 cycloalkyl or aryl(C_1-C_6)alkylene;

R^7 is C_1-C_6 alkyl;

X is a direct link or C_1-C_7 alkylene;

m is 1 or 2; and

n is 0, 1 or 2.

2. A compound as claimed in claim 1 wherein R is phenyl, pyridinyl, pyrimidinyl, thienyl or furyl, each optionally substituted by a group of the formula

$$-X-R^2;$$

R^1 is H, C_1-C_6 alkyl, C_1-C_4 alkoxy(C_1-C_6)alkylene, $R^3R^4NCO(C_1$-C_6)alkylene, or C_3-C_6 cycloalkyl(C_1-C_4)alkylene.

R^2 is COR^7, CO_2R^7, SOR^7, SO_2R^7, $CONR^3R^4$, $SO_2NR^3R^4$, $NHSO_2R^7$, CN or OH.

R^3 and R^4 are either each independently selected from H and C_1-C_4 alkyl, or R^3 and R^4 taken together represent C_3-C_6 alkylene interrupted by O;

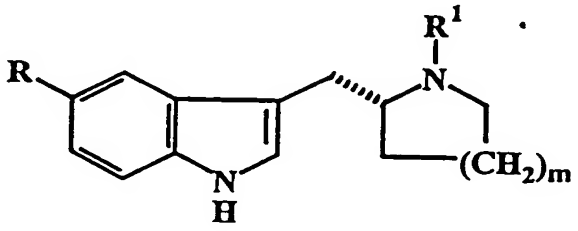
R^7 is methyl, ethyl or n-propyl;

X is a direct link or methylene; and

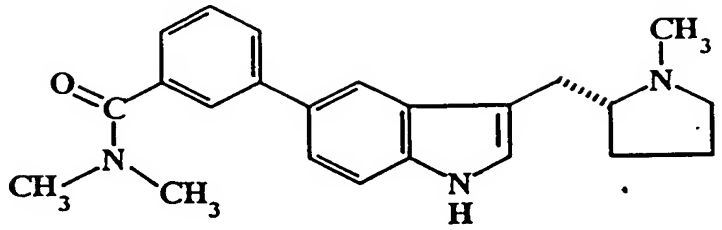
m is 1.

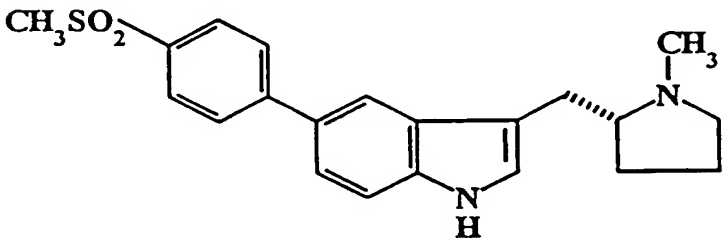
3. A compound as claimed in claim 1 or claim 2 wherein R is phenyl optionally substituted at the 3- or 4-position, or 2-, 3- or 4-pyridinyl optionally substituted at the 5- or 6-position, both optionally substituted with sulphamoyl, N,N-dimethylsulphamoyl, carbamoyl, N-methylcarbamoyl, N,N-dimethylcarbamoyl, morpholinocarbonyl, methyl- or ethyl- or n-propyl-sulphonyl or -sulphinyl, methyl- or ethyl-sulphonylmethyl, acetyl, hydroxymethyl, methoxycarbonyl, ethanesulphonamidomethyl, cyano, carbamoylmethyl, 1-hydroxyprop-2-yl, N,N-dimethylcarbamoylmethyl, ethylcarbamoyl, dimethylcarbamoyl or methoxycarbonyl;
R^1 is hydrogen, methyl, ethyl, 2-methoxyethyl, cyclopropylmethyl, benzyloxycarbonyl, 2-carbamoylethyl, 2-dimethylcarbamoylethyl; and m is 1.

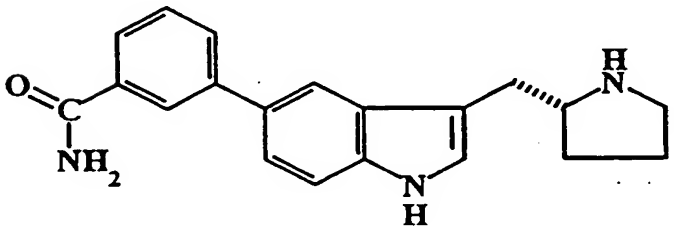
4. A compound as claimed in any of the preceding claims having the R-configuration at the 2-position of the pyrrolidine or piperidine ring, i.e.

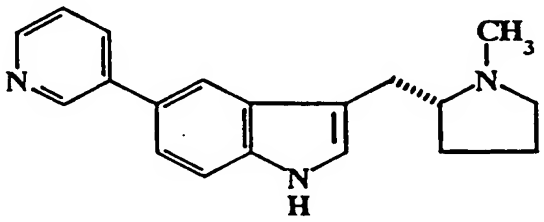


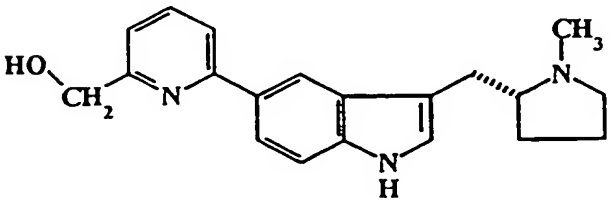
5. A compound of the formula:

(a)  Compound of Example 13 ;

(b)  Compound of Example 1 ;

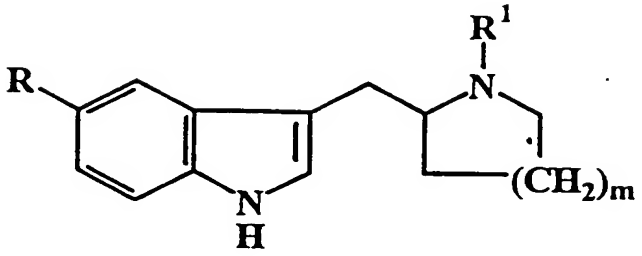
(c)  Compound of Example 38 ;

(d)  Compound of Example 56 ; or

(e)  Compound of Example 63 ;

or a pharmaceutically acceptable salt thereof.

6. A process for the preparation of a compound of the formula:



...(I)

or a pharmaceutically acceptable salt thereof,

wherein R is phenyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, furyl or thienyl, all of which may be optionally substituted by halo, C_1-C_4 alkyl, C_1-C_4 alkoxy or a group of the formula:-

$$-X-R^2 \ ;$$

R^1 is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, C_3-C_6 alkenyl or C_3-C_6 alkynyl, said alkyl group being optionally substituted by C_3-C_7 cycloalkyl, C_3-C_7 cycloalkyloxy, OH, C_1-C_6 alkoxy, $CONR^3R^4$, $SO_2NR^3R^4$, COR^5, SOR^5, SO_2R^5, CO_2R^6, aryl, aryloxy, aryl(C_1-C_6)alkoxy or heteroaryl, said alkenyl group being optionally substituted by aryl and said cycloalkyl group being optionally substituted by OH; the cycloalkyl and cycloalkenyl groups of the foregoing groups being optionally linked to the N-atom by an alkylene moiety;

R^2 is COR^7, CO_2R^7, SOR^7, SO_2R^7, $CONR^3R^4$, $SO_2NR^3R^4$, $NHCOR^7$, $NHCONR^3R^4$, $NHSO_2R^7$, $NHSO_2NR^3R^4$, OH or CN;

R^3 and R^4 are either each independently selected from H, C_3-C_7 cycloalkyl and C_1-C_6 alkyl, said alkyl group being optionally substituted by C_3-C_7 cycloalkyl or aryl,
or R^3 and R^4 taken together represent C_3-C_6 alkylene optionally interrupted by, O, $S(O)_n$, NH or N(C_1-C_6 alkyl);

R^5 is C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkyl(C_1-C_6)alkylene, aryl(C_1-C_6)alkylene; or aryl;

R^6 is C_1-C_6 alkyl, C_3-C_7 cycloalkyl or aryl(C_1-C_6)alkylene;

R^7 is C_1-C_6 alkyl;

X is a direct link or C_1-C_7 alkylene;

m is 1 or 2; and

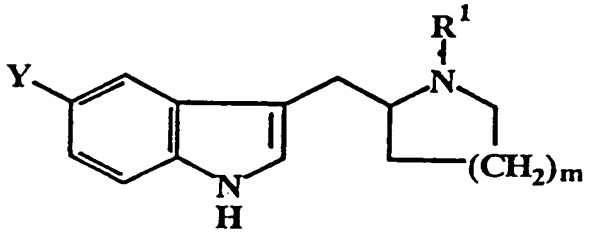
n is 0, 1 or 2.

which comprises:

(a) bringing into a catalysed cross-coupling reaction a compound of formula:

R-M (II)

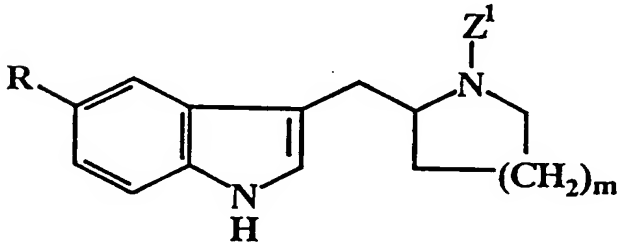
wherein R is as defined for a compound of formula I above and M is an optionally substituted metal substituent suitable for cross-coupling reactions, with a compound of formula:



...(III)

wherein R^1 and m are as defined for a compound of formula (I) and Y is iodo, bromo, or $-OSO_2CF_3$, or

(b) to produce compounds wherein R^1 is hydrogen, removing a protecting group Z^1 from a compound of formula:

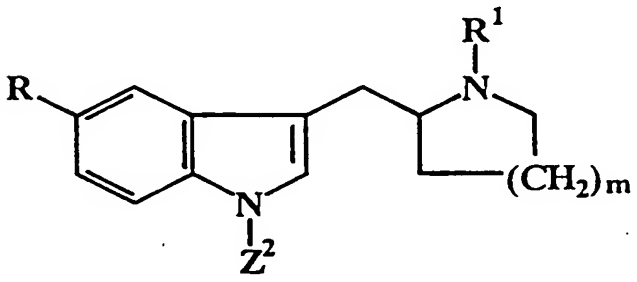


...(X)

wherein R and m are as defined for a compound of formula (I) and Z^1 is a protecting group, or

(c) to produce compounds wherein R^1 is other than hydrogen, bringing into reaction a compound of formula (I) wherein R^1 is hydrogen and R and m are as defined for a compound of formula (I) with a compound serving as an R^1 precursor where R^1 is as defined for a compound of formula (I) but is not hydrogen, or;

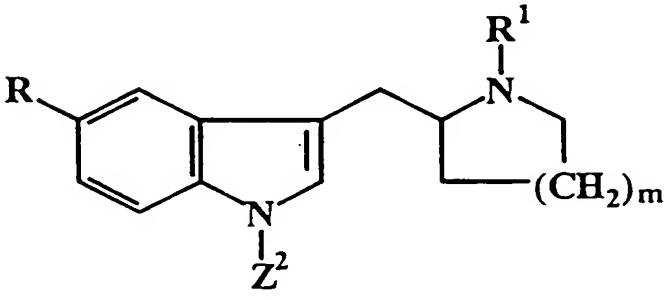
(d) removing a protecting group Z^2 from a compound of formula:



...(XI)

wherein R, R^1 and m are as defined for a compound of formula (I) and Z^2 is a protecting group, or;

(e) to produce compounds of formula (I) wherein R^1 is hydrogen, removing protecting groups R^1, where R^1 is a protecting group Z^1, and Z^2 from a compound of formula:



...(XI)

wherein R and m are as defined for a compound of formula (I); any of said processes (a) to (e) being optionally followed by a conventional functional group transformation within the R or R^1 substituent, or within both, and/or optionally converting the compound of formula (I) into a pharmaceutically acceptable salt thereof.

7. A process as claimed in claim 6, wherein in process (a), M is any of the following:
$(alkyl)_3Sn$-, $(alkyl)_2B$-; $(HO)_2B$-; $(alkoxy)_2B$-, Li-; Cu-; chloroZn-; haloMg-; arylHg- or chloroHg-.

8. A process as claimed in claim 6 or claim 7 wherein in process (a) the reaction is catalysed by a palladium catalyst.

9. A process as claimed in any of claims 6, 7 or 8 wherein, in process (a) a triarylphosphine is present.

10. A process as claimed in claim 6, wherein in process (b) Z^1 is a group $-COOR^8$ where R^8 is t-butyl or benzyl; or Z^1 is as defined for R^1.

11. A process as claimed in claim 6 wherein in process (c) the R^1 precursor is a compound of the formula R^1X wherein R^1 is as defined for a compound of formula (I) and X is a suitable leaving group.

12. A process as claimed in claim 6 wherein in process (d) Z^2 is a protecting group which may be an alkoxy- or benzyloxycarbonyl group or a trialkylsilyl group.

13. A process as claimed in any of claims 6 to 12 wherein:
R is phenyl, pyridinyl, pyrimidinyl, thienyl or furyl and optionally substituted by a group of the formula -X-R^2;

R^1 is H, C_1-C_6 alkyl, C_1-C_4 alkoxy(C_1-C_6)alkylene, $R^3R^4NCO(C_1$-$C_6)$alkylene, or C_3-C_6 cycloalkyl(C_1-C_4)alkylene.

R^2 is COR^7, CO_2R^7, SOR^7, SO_2R^7, $CONR^3R^4$, $SO_2NR^3R^4$, $NHSO_2R^7$, CN or OH;

R^3 and R^4 are either each independently selected from H and C_1-C_4 alkyl, or R^3 and R^4 taken together represent C_3-C_6 alkylene interrupted by O;

R^7 is methyl, ethyl or n-propyl;

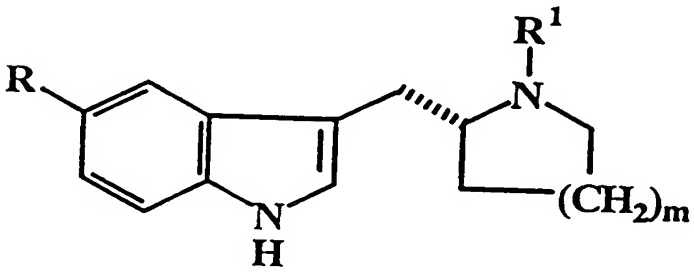
X is a direct link or methylene; and

m is 1.

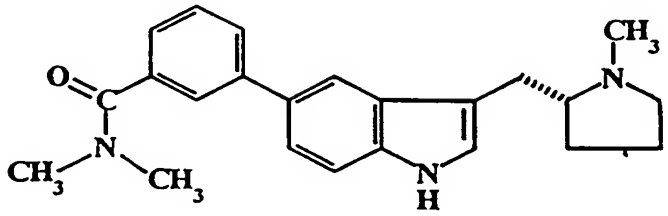
14. A process as claimed in any of claims 6 to 13 wherein R is phenyl optionally substituted at the 3- or 4- position, or 2-, 3- or 4-pyridinyl optionally substituted at the 5- or 6- position, both optionally substituted with sulphamoyl, N,N-dimethylsulphamoyl, carbamoyl, N-methylcarbamoyl, N,N-dimethylcarbamoyl, morpholinocarbonyl, methyl- or ethyl- or n-propyl-sulphonyl or -sulphinyl, methyl- or ethyl-sulphonylmethyl, acetyl, hydroxymethyl, methoxycarbonyl, ethanesulphonamidomethyl, cyano, carbamoylmethyl, 1-hydroxyprop-2-yl, N,N-dimethylcarbamoylmethyl, ethylcarbamoyl, dimethylcarbamoyl, or methoxycarbonyl;

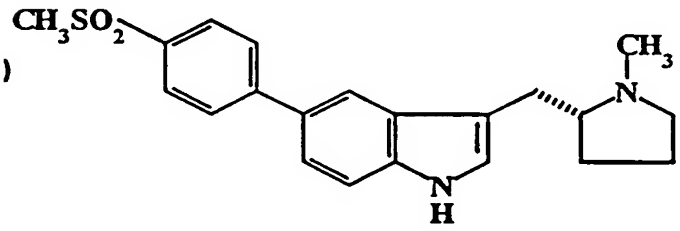
R^1 is hydrogen, methyl, ethyl, 2-methoxyethyl, cyclopropylmethyl, benzyloxycarbonyl, 2-carbamoylethyl, 2-dimethylcarbamoylethyl; and m is 1.

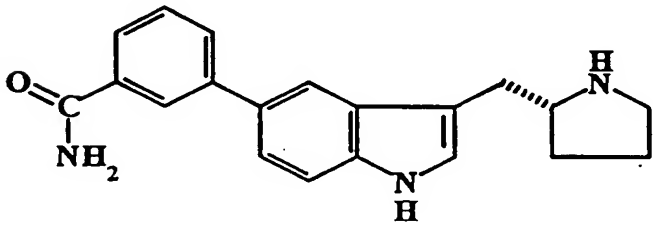
15. A process as claimed in any of claims 6 to 14 wherein the said compound of formula (I) produced is the stereoisomer having the R-configuration of formula:

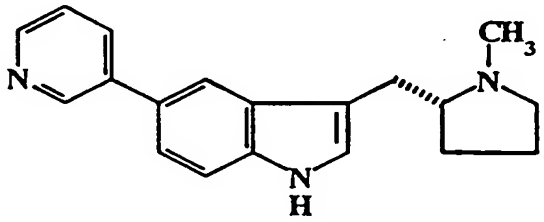


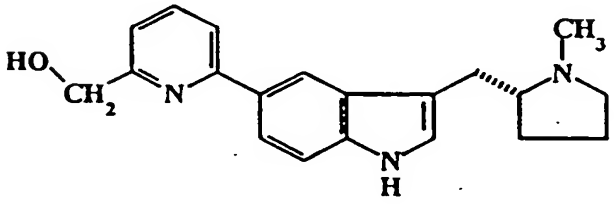
16. A process as claimed in claim 15 wherein a compound of the formula:

(a)  Compound of Example 13 ;

(b)  Compound of Example 1 ;

(c)  Compound of Example 38 ;

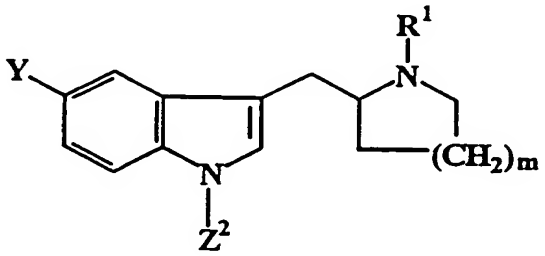
(d)  Compound of Example 56 ; or

(e)  Compound of Example 63 ;

or a pharmaceutically acceptable salt thereof, is prepared

17. An novel intermediates the compounds of formulae (IX), (X), (XI) and (XIII) as hereinbefore described; and, for (X) and (XI), as defined in claim 6.

18. A compound having the formula:



...(XIV)

and useful as an intermediate to prepare the compounds claimed in claim 1, and

wherein R^1 is as defined in claim 1 or is a protecting group Z^1 where Z^1 is an arylalkoxycarbonyl, benzyloxycarbonyl or alkoxycarbonyl group, preferably a t-butyloxycarbonyl group;
Y is $(alkyl)_3Sn$-; $(alkyl)_2B$-; $(HO)_2B$-; $(alkoxy)_2B$-; Li-; Cu-; chloroZn-; haloMg-; arylHg- or chloroHg-; and
Z^2 is a trialkylsilyl or alkoxycarbonyl group.

19. A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any of claims 1 to 5, together with a pharmaceutically acceptable diluent or carrier.

20. A compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, as claimed in any of claims 1 to 5 or claim 19, respectively, for use in medicine.

21. The use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, as claimed in any of claims 1 to 5, or claim 19, respectively, for the manufacture of a medicament for the curative or prophylactic treatment of migraine or an associated condition such as cluster headache, chronic paroxysmal hemicrania or headache associated with a vascular disorder, or of depression, anxiety, an eating disorder, obesity or drug abuse.

22. The use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, as claimed in any of claims 1 to 5, or claim 19, respectively, for the manufacture of a medicament for the curative or prophylactic treatment of a medical condition for which a selective agonist of 5-HT_1-like receptors is indicated.

23. A method of treating a human being to cure or prevent migraine or an associated condition such as cluster headache, chronic paroxysmal hemicrania or headache associated with a vascular disorder, or depression, anxiety, an eating disorder, obesity or drug abuse, which comprises treating said human being with an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, as claimed in any of claims 1 to 5, or claim 19, respectively.

24. A method of treating a human being to cure or prevent a medical condition for which a selective agonist of 5-HT_1-like receptors is indicated, which comprises treating said human being with an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, as claimed in any of claims 1 to 5, or claim 19, respectively.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 93/00867

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D403/06; A61K31/40; C07D401/14; C07D403/14
C07D409/14; C07D407/14

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	WO,A,9 118 897 (THE WELLCOME FOUNDATION LTD) 12 December 1991 see claims	1,19
P,A	WO,A,9 206 973 (PFIZER INC.) 30 April 1992 see claims	1,19

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
25 JUNE 1993	- 8. 07. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	VAN BIJLEN H.

INTERNATIONAL SEARCH REPORT

.ational application No.
PCT/EP 93/00867

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 23 + 24 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

EP 9300867
SA 72345

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 25/06/93

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9118897	12-12-91	AU-A- 7957091	31-12-91
		EP-A- 0486666	27-05-92
WO-A-9206973	30-04-92	AU-A- 8950491	20-05-92
		CN-A- 1062529	08-07-92